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(71) Applicants and

(72) Inventors: SAUS, Juan [ES/ES]; Calle Conde de Altea  
8-7a, E-46005 Valencia (ES). REVERT-ROS, Francisco  
[ES/ES]; C/Sanchis Sivera, 27, 6a, E-46008 Valencia (ES).

(74) Agents: VOSSIUS, Volker et al.; Patent- und Rechts-,  
Geibelstrasse 6, 81679 München (DE).

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(54) Title: GIPs, A FAMILY OF POLYPEPTIDES WITH TRANSCRIPTION FACTOR ACTIVITY THAT INTERACT WITH  
GOODPASTURE ANTIGEN BINDING PROTEIN

(57) Abstract: The present invention provides isolated GPBP-interacting 90 and 130 kDa polypeptides, and portions thereof (GIP90/130 polypeptides), antibodies to the GIP90/130 polypeptides, and pharmaceutical compositions thereof. The present invention also provides isolated GIP90/130 nucleic acid sequences, expression vectors comprising the nucleic acid sequences, and host cells transfected with the expression vectors. The invention further provides methods for detecting the GIP90/130 polypeptides or nucleic acid sequences, methods for inhibiting interactions between GPBP and GIP90/130 polypeptides, between pol k76 and GIP90/130 polypeptides or aggregation of GIP90/130 polypeptides, and methods for treating patients with autoimmune disorders or cancer.

WO 03/048193 A2

**GIPs, a Family of Polypeptides with Transcription Factor Activity that Interact  
with Goodpasture Antigen Binding Protein**

**Field of the invention**

The present invention is in the general fields of molecular biology, cell biology, protein-protein interactions, autoimmunity, cancer, and drug discovery.

**Background**

Goodpasture antigen binding protein (GPBP) is a ubiquitous protein kinase with a  $M_r$  of 80-89 kDa that is preferentially expressed in tissues and cells that are common targets of autoimmune responses, such as the Langerhans islets (type I diabetes); the white matter of the central nervous system (multiple sclerosis); the biliary ducts (primary biliary cirrhosis); the cortical cells of the adrenal gland (Addison disease); striated muscle cells (myasthenia gravis); spermatogonium (male infertility); Purkinje cells of the cerebellum (paraneoplastic cerebellar degeneration syndrome); and intestinal epithelial cells (pernicious anemia, autoimmune gastritis and enteritis).

GPBP is expressed as two isoforms (GPBP and GPBP $\Delta$ 26) which result from exon alternative splicing of the corresponding pre-mRNA. GPBP is the more active variant, and its expression is still more restricted to histological structures targeted by common autoimmune responses including human alveolar and glomerular basement membranes (Goodpasture disease). GPBP binds to and phosphorylates the human  $\alpha$ 3 NC1 domain of type IV collagen ( $\alpha$ 3(IV)NC1) also called the Goodpasture antigen (WO 00/50607), as this domain is the target of the pathogenic autoantibodies mediating the Goodpasture autoimmune response. Phosphorylation activates the  $\alpha$ 3(IV)NC1 domain for aggregation, a process that is catalyzed at least in part by GPBP and which comprises conformational isomerization reactions and disulfide-bond exchange (WO 02/061430).

An augmented expression of GPBP with respect to GPBPA26 has been associated with the production of non-tolerized, aberrant conformational versions of the human  $\alpha 3(\text{IV})\text{NC1}$  domain ("aberrant conformers") and the subsequent autoantibody production that causes Goodpasture disease (WO 02/061430). The evidence suggests that a similar pathogenic mechanism is involved in other autoimmune conditions, including cutaneous lupus erythematosus, pemphigus, pemphigoid and lichen planus, and that aberrant GPBP expression and autoimmune pathogenesis are related processes. Furthermore, GPBP is down-regulated in cancer cell lines (WO 00/50607), suggesting that the cell machinery harboring GPBP/GPBPA26 is also involved in signaling pathways that decrease cell division or induce cell death. These pathways could be up regulated during autoimmune pathogenesis to cause altered antigen presentation in individuals carrying specific MHC haplotypes, and down regulated during cell transformation to prevent autoimmune attack of the transformed cells during tumor growth.

Based on all of the above, there exists a need in the art to identify methods and reagents for modifying GPBP activity for use in treating autoimmune disorders and cancer.

### Summary of the Invention

In one aspect, the present invention provides isolated GPBP-interacting 90 and 130 kDa polypeptides, and portions thereof (GIP90/130 polypeptides), antibodies to the GIP 90/130 polypeptides, and pharmaceutical compositions thereof. In a further aspect, the present invention provides isolated GIP90/130 nucleic acid sequences, expression vectors comprising the nucleic acid sequences, and host cells transfected with the expression vectors. The invention further provides methods for detecting the GIP90/130 polypeptides or nucleic acid sequences, methods for modifying interactions between GPBP and GIP90/130 polypeptides, aggregation of GIP90/130 polypeptides, and GIP90/130 polypeptide-mediated gene transcription, and methods for treating patients with autoimmune disorders or cancer.

### Brief Description of the Figures

Figure 1 is a diagram of the exon-intron structure of the GIP90 genomic DNA as determined by BLAST search against Human Genome NCBI in May 20, 2002.

Figure 2 is a representation of differences between various GIP90/130 mRNA and polypeptide species.

Figure 3 is a sequence alignment of the full length GIP90/130 polypeptides and DOC1 and DOC1-related protein.

- 5 Figure 4 is the amino acid sequence of I-20. Residues in bold font are those identified as essential for interactions between GIP90/130 and GPBP; in small letters are other residues identified as participating in interaction between GIP90/130 and GPBP, but not essential; and underlined are the residues implicated in GIP90/130 aggregation.

## 10 DETAILED DESCRIPTION OF THE INVENTION

Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P. Deutscher, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2<sup>nd</sup> Ed.* (R.I. Freshney. 1987, Liss, Inc. New York, NY), *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.), and the Ambion 1998 Catalog (Ambion, Austin, TX).

As used herein, the term "GIP90/130" and "GIP90/130 polypeptide(s)" refers to the family of GPBP-interacting proteins that includes GIP90, GIP130a, GIP130b, and GIP130c, amino acid sequences derived therefrom, and includes both monomers and 25 oligomers thereof.

As used herein, the term "GIP90" refers to the 90 kDa form of GIP, which consists of the amino acid sequence of SEQ ID NO:10, and includes both monomers and oligomers thereof.

As used herein, the term "GIP130a" refers to one of the 130 kDa forms of GIP, 30 which consists of the amino acid sequence of SEQ ID NO:12, and includes both monomers and oligomers thereof.

As used herein, the term "GIP130b" refers to one of the 130 kDa forms of GIP, which consists of the amino acid sequence of SEQ ID NO:14, and includes both monomers and oligomers thereof.

As used herein, the term "GIP130c" refers to one of the 130 kDa forms of GIP, which consists of the amino acid sequence of SEQ ID NO:16, and includes both monomers and oligomers thereof.

5 The numbering of nucleotides and residues used below for GIP proteins refer to the GenBank accession number AF329092.

As used herein, the term "DOC proteins" or "DOC1 proteins" refers to down regulated in ovarian cancer-1 (DOC1) (Genbank accession number NM 014890) and DOC1-related protein (Genbank accession number BC027860). DOC1 and DOC1-related protein are derived from the same gene since they are identical in the homology  
10 region at nucleotide and amino acid levels

As used herein, the term "GPBP" refers to Goodpasture antigen binding protein, and includes both monomers and oligomers thereof, as disclosed in WO 00/50607.

As used herein, the term "GPBPΔ26" refers to the Goodpasture antigen binding protein alternatively spliced product deleted for 26 amino acid residues as disclosed in  
15 WO 00/50607, and includes both monomers and oligomers thereof.

As used herein pol  $\kappa$  means the primary protein product of the *POLK* as disclosed in WO 02/46378.

As used herein, pol  $\kappa$ 76 means the 76 kDa alternatively spliced isoform product of the *POLK* as disclosed in WO 02/46378.

20 As used herein, "aggregation" refers to both self-aggregation of an individual GIP90/130 polypeptide, and aggregation of two or more different GIP90/130 polypeptides.

In one aspect, the present invention provides isolated GIP90/130 polypeptides. In one embodiment, the isolated GIP90/130 polypeptide comprises at least 6 amino acids  
25 of the amino acid sequence of SEQ ID NO:2, which is a unique 10 amino acid polypeptide (SYRRILGQLL) that is herein demonstrated to be essential for the interaction between GIP90/130 and GPBP (discussed in detail below), and is not present in DOC proteins. In further embodiments, the isolated GIP90/130 polypeptide comprises at least 7, 8, 9, or 10 amino acids of the amino acid sequence of SEQ ID NO:2. In still further embodiments,  
30 the isolated GIP90/130 polypeptide consists of at least 6, 7, 8, 9, or 10 amino acids of the amino acid sequence of SEQ ID NO:2. These polypeptides can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides or to raise antibodies that interfere with GPBP-GIP90/130 interaction.

In further embodiments, the isolated GIP90/130 polypeptide comprises and/or consists of the amino acid sequence of SEQ ID NO:4, which is the N-terminal region of GIP90/130a/c that is not present in DOC proteins (described in detail below), and which is encoded by exon II-IV and part of exon V (Figure 3). These polypeptides are thus useful, for example, to develop reagents, such as antibodies, that can distinguish between GIP90/130 and DOC proteins. This polypeptide includes sequences implicated in the interaction between GPBP and GIP90/130 (including SEQ ID NO:2), and thus can be used (or antibodies to the polypeptides can be used), for example, to modify interactions between GPBP and GIP90/130 polypeptides. This polypeptide also includes sequences implicated in GIP90/130 aggregation, and thus can further be used (or antibodies to the polypeptides can be used) to modify GIP90/130 aggregation. This polypeptide also includes sequences implicated in the transcriptional activity of GIP90/130 and thus the polypeptides, or antibodies derived therefrom, can be further used for modulating specific gene expression.

The polypeptides of the invention also include polypeptides comprising and/or consisting of the amino acid sequence of SEQ ID NO:6, which is referred to as I-20, a 265 amino acid polypeptide that is described in detail below. This polypeptide interacts more strongly with GPBP and pol  $\kappa$ 76 than the full length GIP90/130 polypeptides, and aggregates more efficiently than the full length GIP90/130 polypeptides. Furthermore, I-20 does not induce gene transcription, in contrast to the full length GIP90/130 polypeptides. Therefore this polypeptide can be used (or antibodies to the polypeptides can be used), for example, to modify (a) interactions between GPBP and GIP90/130 polypeptides; (b) interactions between pol  $\kappa$ 76 and GIP90/130 polypeptides; (c) GIP90/130 polypeptide aggregation; and (d) other functions of the GIP90/130 polypeptides, such as induction of gene transcription.

The polypeptides of the invention also include polypeptides comprising and/or consisting of the amino acid sequence of SEQ ID NO:8, which consists of the N-terminus of GIP90 to the end of I-20, and is encoded by exons II-IV and part of exon V up to the end of the I-20 coding sequence. This polypeptide includes sequences implicated in (a) the interaction between GPBP and GIP90/130 polypeptides, (b) GIP90/130 polypeptide aggregation, and (c) the transcriptional activity of GIP90/130 polypeptides, and thus the polypeptides, or antibodies derived therefrom, can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides, to modify GIP90/130 aggregation, and to modulate gene expression.

The polypeptides of the invention also include polypeptides comprising and/or consisting of the amino acid sequence of SEQ ID NO:10 (GIP90), SEQ ID NO:12 (GIP130a), SEQ ID NO:14 (GIP130b), or SEQ ID NO:16 (GIP130c). These full length polypeptides, described in more detail below, interact with GPBP and are capable of aggregation. These polypeptides can be used, for example, to modify GPBP-GIP90/130 interactions, to modify GIP90/130 aggregation, to modulate gene expression, as well as for other purposes described herein.

In a further embodiment, the isolated GIP 90/130 polypeptide comprises at least 8 amino acids of the amino acid sequence of SEQ ID NO:18, which is a unique 15 amino acid peptide that is present at the C-terminus of GIP90 and is not present in DOC proteins, GIP130a, GIP130b, or GIP130c, and thus can be used, for example, to generate reagents, such as antibodies, to distinguish GIP90 from other members of the GIP90/130 polypeptide family. Furthermore, the polypeptides, or antibodies thereto, can be used to specifically modify GIP90 self-aggregation. In further embodiments, the isolated GIP90/130 polypeptide comprises or consists of at least 9, 10, 11, 12, 13, 14, or 15 amino acids of the amino acid sequence of SEQ ID NO:18.

In a further embodiment, the isolated GIP90/130 polypeptide consists of at least 8 amino acids of the amino acid sequence of SEQ ID NO:20, which is a 30 amino acid polypeptide present within I-20 that has been implicated in the interaction of GIP90/130 with GPBP and also in GIP90/130 aggregation. In further embodiments, the isolated GIP90/130 polypeptide consists of at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acids the amino acid sequence of SEQ ID NO:20. Thus, these polypeptides, or antibodies to the polypeptides, can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides. Furthermore, since this polypeptide is present in each of GIP90, GIP130a, GIP130b, GIP130c, and DOC1 proteins, these polypeptides, or antibodies thereto, can be used to generally modify aggregation of the GIP90/130 polypeptides and DOC1 proteins. Despite the fact that DOC1 proteins contain SEQ ID NO:20, they do not interact in a two hybrid assay with GPBP (see below), and thus SEQ ID NO:20, while implicated in the interaction of GIP90/130 polypeptides and GPBP, is not sufficient for GPBP interaction.

In a still further embodiment, the isolated GIP90/130 polypeptide comprises or consists of the amino acid sequence of SEQ ID NO:22, which is a unique 386 amino acid polypeptide that is present at the C-terminus of GIP130a but is not present in GIP90, is not wholly present in DOC1, and includes variations from GIP130b, GIP130c, and DOC1-



related protein, and thus can be used, for example, to modify GIP130a aggregation, and to generate reagents, such as antibodies, to distinguish GIP130a from other members of the GIP90/130 polypeptide family, and the DOC proteins. This region contains sequences that down-regulate GIP 90/130 interaction with GPBP which can be used to modify  
5 GIP90/130-GPBP interaction, or to generate reagents, such as antibodies for the same purposes.

In a still further embodiment, the isolated GIP90/130 polypeptide comprises or consists of the amino acid sequence of SEQ ID NO:24, which is GIP130a deleted from the N-terminus to the end of I-20. This polypeptide lacks critical regions of the GIP90/130  
10 polypeptides implicated in GPBP interaction and induction of gene expression, and like the C terminus of GIP130b/c contains amino acid sequences that down-regulate interaction with GPBP. Thus, the polypeptides, or antibodies thereto, can be used, for example, to modify GPBP-GIP90/130 polypeptide interactions or to modify GIP90/130 polypeptide aggregation.

In a still further embodiment, the isolated GIP 90/130 polypeptide comprises or consists of the amino acid sequence of SEQ ID NO:26, which is a unique 7 amino acid polypeptide present at the C-terminus of GIP130a, and is not present in any of GIP90, GIP130b, GIP130c, and DOC proteins. Thus, these polypeptides can be used to produce reagents, such as antibodies, that are specific for GIP130a, and which can be used, for  
20 example, to specifically modify GIP130a aggregation.

In another embodiment, the isolated GIP90/130 polypeptide comprises at least 6 amino acids of the amino acid sequence of SEQ ID NO:28, which is a unique 10 amino acid polypeptide (LDKVVEKHKE) within I-20 that participates in interactions between GIP90/130 polypeptides and GPBP, is essential for GIP90/130 polypeptide aggregation,  
25 and is not present in DOC proteins. In further embodiments, the isolated GIP90/130 polypeptide comprises or consists of at least 7, 8, 9, or 10 amino acids of the amino acid sequence of SEQ ID NO:28. These polypeptides or antibodies raised against them can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides or to modify GIP90/130 polypeptide aggregation.

In another embodiment, the isolated GIP90/130 polypeptide consists of at least 6 amino acids of the amino acid sequence of SEQ ID NO:30, which is an 10 amino acid polypeptide (EEEQKATRLE) within I-20 that participates in interactions between GIP90/130 polypeptides and GPBP, is essential for GIP90/130 polypeptide aggregation,  
30 and is present in DOC proteins. In further embodiments, the isolated GIP90/130

polypeptide consists of at least 7, 8, 9, or 10 amino acids of the amino acid sequence of SEQ ID NO:30. These polypeptides or antibodies raised against them can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides or to modify GIP90/130 polypeptide aggregation. Furthermore, since this polypeptide is present in each of GIP90, GIP130a, GIP130b, GIP130c, and DOC1 proteins, these polypeptides, or antibodies thereto, can be used to generally modify aggregation of the GIP90/130 polypeptides and DOC1/DOC1-related proteins. Despite the fact that DOC1 proteins contain SEQ ID NO:20, they do not interact in a two hybrid assay with GPBP (see below), and thus SEQ ID NO:20, while implicated in the interaction of GIP90/130 polypeptides and GPBP, is not sufficient for GPBP interaction.

In another embodiment, the isolated GIP90/130 polypeptide comprises at least 8 amino acids of the amino acid sequence of SEQ ID NO:32, which is a unique 20 amino acid polypeptide (LDKVVEKHKESYRRILGQLL) within I-20 that contains essential residues for the interaction between GIP90/130 polypeptides and GPBP and for GIP90/130 polypeptide aggregation, and is not present in DOC proteins. In further embodiments, the isolated GIP90/130 polypeptide comprises or consists of at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids of the amino acid sequence of SEQ ID NO:32. These polypeptides can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides and to modify GIP90/130 polypeptide aggregation, or to raise antibodies that modify interactions between GPBP and GIP90/130 polypeptides and to modify GIP90/130 polypeptide aggregation.

In another embodiment, the isolated GIP90/130 polypeptide consists of at least 8 amino acids of the amino acid sequence of SEQ ID NO:34, which is a 50 amino acid polypeptide that is contained within I-20, contains regions essential for the interaction between GIP90/130 polypeptides and GPBP and for GIP90/130 polypeptide aggregation, and is present in DOC proteins. In further embodiments, the isolated GIP90/130 polypeptide consists of at least 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 amino acids of the amino acid sequence of SEQ ID NO:34. These polypeptides can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides and to modify GIP90/130 polypeptide aggregation, or to raise antibodies that modify interactions between GPBP and GIP90/130 polypeptides and to modify GIP90/130 polypeptide aggregation. Furthermore, since this polypeptide is present in each of GIP90, GIP130a, GIP130b, GIP130c, and DOC1 proteins, these polypeptides, or antibodies

thereto, can be used to generally modify aggregation of the GIP90/130 polypeptides and DOC1/DOC1-related proteins. Despite the fact that DOC1 proteins contain SEQ ID NO:20, they do not interact in a two hybrid assay with GPBP (see below), and thus SEQ ID NO:20, while implicated in the interaction of GIP90/130 polypeptides and GPBP, is not  
5 sufficient for GPBP interaction.

The polypeptides of the invention also include polypeptides comprising and/or consisting of the amino acid sequence of SEQ ID NO:36, which consists of the first 240 amino acids of the N-terminus of GIP130b, which is not present in DOC1 proteins, and which differs from the corresponding sequence in GIP90, GIP130a, and GIP130c by a  
10 single amino acid residue at position 168. This polypeptide includes sequences implicated in (a) the interaction between GPBP and GIP90/130 polypeptides, (b) GIP90/130 polypeptide aggregation, and (c) the transcriptional activity of GIP90/130 polypeptides, and thus the polypeptides, or antibodies derived therefrom, can be used, for example, to modify interactions between GPBP and GIP90/130 polypeptides, to  
15 modify GIP90/130 aggregation, and to modulate gene expression.

In a still further embodiment, the isolated GIP 90/130 polypeptide consists of the amino acid sequence of SEQ ID NO:38 which is a unique 384 amino acid polypeptide that is present at the C terminus of GIP130b/c and DOC1-related protein but is not present in GIP90, is not wholly present in DOC1, and includes variations from GIP130a, and thus  
20 can be used, for example, to modify GIP130b/c aggregation, and to generate reagents, such as antibodies, to distinguish GIP130b/c and the DOC1-related protein from other members of the GIP90/130 polypeptide family.

As used herein, an "isolated polypeptide" refers to a polypeptide that is substantially free of other proteins, cellular material and culture medium when isolated  
25 from cells or produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Thus, the protein can either be purified from natural sources, chemically synthesized, or recombinant protein can be purified from the recombinant host cells disclosed below.

Synthetic polypeptides, prepared using the well known techniques of solid  
30 phase, liquid phase, or peptide condensation techniques, or any combination thereof, can include natural and unnatural amino acids. Amino acids used for peptide synthesis may be standard Boc (N $\alpha$ -amino protected N $\alpha$ -t-butyloxycarbonyl) amino acid resin with the standard deprotecting, neutralization, coupling and wash protocols of the original solid phase procedure of Merrifield (1963, J. Am. Chem. Soc. 85:2149-2154),

or the base-labile N $\alpha$ -amino protected 9-fluorenylmethoxycarbonyl (Fmoc) amino acids first described by Carpino and Han (1972, J. Org. Chem. 37:3403-3409). Both Fmoc and Boc N $\alpha$ -amino protected amino acids can be obtained from Sigma, Cambridge Research Biochemical, or other chemical companies familiar to those skilled in the art.

- 5 In addition, the polypeptides can be synthesized with other N $\alpha$ -protecting groups that are familiar to those skilled in this art.

Solid phase peptide synthesis may be accomplished by techniques familiar to those in the art and provided, for example, in Stewart and Young, 1984, Solid Phase Synthesis, Second Edition, Pierce Chemical Co., Rockford, Ill.; Fields and Noble, 1990,  
10 Int. J. Pept. Protein Res. 35:161-214, or using automated synthesizers. The polypeptides of the invention may comprise D-amino acids (which are resistant to L-amino acid-specific proteases in vivo), a combination of D- and L-amino acids, and various "designer" amino acids (e.g.,  $\beta$ -methyl amino acids, C $\alpha$ -methyl amino acids, and N $\alpha$ -methyl amino acids, etc.) to convey special properties. Synthetic amino acids  
15 include ornithine for lysine, fluorophenylalanine for phenylalanine, and norleucine for leucine or isoleucine.

In addition, the polypeptides can have peptidomimetic bonds, such as ester bonds, to prepare peptides with novel properties. For example, a peptide may be generated that incorporates a reduced peptide bond, i.e., R<sub>1</sub>-CH<sub>2</sub>-NH-R<sub>2</sub>, where R<sub>1</sub> and  
20 R<sub>2</sub> are amino acid residues or sequences. A reduced peptide bond may be introduced as a dipeptide subunit. Such a polypeptide would be resistant to protease activity, and would possess an extended half-life in vivo.

Alternatively, the proteins are produced by the recombinant host cells disclosed below, and purified using standard techniques. (See for example, *Molecular Cloning:*  
25 *A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press.)) The protein can thus be purified from prokaryotic or eukaryotic sources. In various further preferred embodiments, the protein is purified from bacterial, yeast, or mammalian cells.

The protein may comprise additional sequences useful for promoting  
30 purification of the protein, such as epitope tags and transport signals. Examples of such epitope tags include, but are not limited to FLAG (Sigma Chemical, St. Louis, MO), myc (9E10) (Invitrogen, Carlsbad, CA), 6-His (Invitrogen; Novagen, Madison, WI), and HA (Boehringer Mannheim Biochemicals). Examples of such transport signals include,

but are not limited to, export signals, secretory signals, nuclear localization signals, and plasma membrane localization signals.

In another aspect, the present invention provides antibodies against the GIP90/130 polypeptides disclosed herein. Such antibodies can be used in a manner  
5 similar to the polypeptides they recognize in modifying GPBP-GIP90/130 interactions, modifying GIP90/130 aggregation, and/or modifying GIP90/130-mediated transcriptional activity. Furthermore, such antibodies can be used to distinguish between members of the GIP90/130 family, as discussed above.

In one embodiment, the antibodies are directed against an epitope present in a  
10 polypeptide of one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:18, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:32, and SEQ ID NO:36. In a further embodiment, the antibodies are directed against an amino acid sequence selected from the group consisting of SEQ  
ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID  
15 NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO: 28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, and SEQ ID NO:38.

Antibodies can be made by well-known methods, such as described in Harlow  
and Lane, Antibodies; A Laboratory Manual, Cold Spring Harbor Laboratory, Cold  
20 Spring Harbor, N.Y., (1988). In one example, pre-immune serum is collected prior to the first immunization. A peptide portion of the amino acid sequence of a GIP90/130 polypeptide, together with an appropriate adjuvant, is injected into an animal in an amount and at intervals sufficient to elicit an immune response. Animals are bled at  
regular intervals, preferably weekly, to determine antibody titer. The animals may or  
25 may not receive booster injections following the initial immunization. At about 7 days after each booster immunization, or about weekly after a single immunization, the animals are bled, the serum collected, and aliquots are stored at about -20° C. Polyclonal antibodies against GIP90/130 polypeptides can then be purified directly by  
passing serum collected from the animal through a column to which non-antigen-related  
30 proteins prepared from the same expression system without GIP90/130 polypeptides bound.

Monoclonal antibodies can be produced by obtaining spleen cells from the animal. (See Kohler and Milstein, Nature 256, 495-497 (1975)). In one example, monoclonal antibodies (mAb) of interest are prepared by immunizing inbred mice with

a GIP90/130 polypeptide, or portion thereof. The mice are immunized by the IP or SC route in an amount and at intervals sufficient to elicit an immune response. The mice receive an initial immunization on day 0 and are rested for about 3 to about 30 weeks. Immunized mice are given one or more booster immunizations of by the intravenous (IV) route. Lymphocytes from antibody positive mice are obtained by removing spleens from immunized mice by standard procedures known in the art. Hybridoma cells are produced by mixing the splenic lymphocytes with an appropriate fusion partner under conditions which will allow the formation of stable hybridomas. The antibody producing cells and fusion partner cells are fused in polyethylene glycol at concentrations from about 30% to about 50%. Fused hybridoma cells are selected by growth in hypoxanthine, thymidine and aminopterin supplemented Dulbecco's Modified Eagles Medium (DMEM) by procedures known in the art. Supernatant fluids are collected from growth positive wells and are screened for antibody production by an immunoassay such as solid phase immunoradioassay. Hybridoma cells from antibody positive wells are cloned by a technique such as the soft agar technique of MacPherson, Soft Agar Techniques, in Tissue Culture Methods and Applications, Kruse and Paterson, Eds., Academic Press, 1973.

To generate such an antibody response, a GIP90/130 polypeptide or portion thereof is typically formulated with a pharmaceutically acceptable carrier for parenteral administration. Such acceptable adjuvants include, but are not limited to, Freund's complete, Freund's incomplete, alum-precipitate, water in oil emulsion containing *Corynebacterium parvum* and tRNA. The formulation of such compositions, including the concentration of the polypeptide and the selection of the vehicle and other components, is within the skill of the art.

The term antibody as used herein is intended to include antibody fragments thereof which are selectively reactive with GIP90/130 polypeptides. Antibodies can be fragmented using conventional techniques, and the fragments screened for utility in the same manner as described above for whole antibodies. For example,  $F(ab')_2$  fragments can be generated by treating antibody with pepsin. The resulting  $F(ab')_2$  fragment can be treated to reduce disulfide bridges to produce Fab' fragments.

In another aspect, the present invention provides isolated nucleic acids that encode GIP90/130 polypeptides. In one embodiment, the isolated nucleic acid sequences comprise sequences encoding an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID

NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO: 28, SEQ ID NO:32, and SEQ ID NO:36. In a further embodiment, the isolated nucleic acid sequences consist of sequences encoding an amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO: 28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, and SEQ ID NO:38.

In another embodiment, the isolated nucleic acids comprise sequences that hybridize under high stringency conditions to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35, their complement, or their transcription product. Stringency of hybridization is used herein to refer to conditions under which nucleic acid hybrids are stable. As known to those of skill in the art, the stability of hybrids is reflected in the melting temperature ( $T_M$ ) of the hybrids.  $T_M$  decreases approximately 1-1.5°C with every 1% decrease in sequence homology. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is performed under conditions of lower stringency, followed by washes of varying, but higher, stringency. Reference to hybridization stringency relates to such washing conditions. Thus, as used herein, high stringency refers to conditions that permit hybridization of those nucleic acid sequences that form stable hybrids in 0.1% SSPE at 65°C. It is understood that these conditions may be duplicated using a variety of buffers and temperatures and that they are not necessarily precise. Denhardt's solution and SSPE (see, e.g., Sambrook, Fritsch, and Maniatis, in: Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1989) are well known to those of skill in the art, as are other suitable hybridization buffers.

In another embodiment, the isolated nucleic acids comprise one or more sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35, their complement, or their transcription product. In a further embodiment, the isolated nucleic acid sequences comprise one or more sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID

NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35, their complement, or their transcription product. In a further embodiment, the isolated nucleic acid sequences consist of one or more sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, and SEQ ID NO:37, their complement, or their transcription product.

As used herein, an "isolated nucleic acid sequence" refers to a nucleic acid sequence that is free of gene sequences which naturally flank the nucleic acid in the genomic DNA of the organism from which the nucleic acid is derived (i.e., genetic sequences that are located adjacent to the gene for the isolated nucleic molecule in the genomic DNA of the organism from which the nucleic acid is derived). An "isolated" GIP90/130 nucleic acid sequence according to the present invention may, however, be linked to other nucleotide sequences that do not normally flank the recited sequence, such as a heterologous promoter sequence, or other vector sequences. It is not necessary for the isolated nucleic acid sequence to be free of other cellular material to be considered "isolated", as a nucleic acid sequence according to the invention may be part of an expression vector that is used to transfect host cells (see below).

In all of these embodiments, the isolated nucleic acid sequence may comprise RNA or DNA, and may be single stranded or double stranded. Such single stranded sequences can comprise the disclosed sequence, its complement, or the transcription product thereof. The isolated sequence may further comprise additional sequences useful for promoting expression and/or purification of the encoded protein, including but not limited to polyA sequences, modified Kozak sequences, and sequences encoding epitope tags, export signals, and secretory signals, nuclear localization signals, and plasma membrane localization signals.

In another embodiment, the present invention provides an expression vector comprising an isolated nucleic acid as described above, operatively linked to a promoter. In a preferred embodiment, the promoter is heterologous (i.e.: is not the naturally occurring GIP90/130 promoter). A promoter and a GIP90/130 nucleic acid sequence are "operatively linked" when the promoter is capable of driving expression of the GIP90/130 DNA into RNA.



As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA into which additional DNA segments may be cloned. Another type of vector is a viral vector, wherein additional DNA segments may be cloned into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors), are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of nucleic acid sequences to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" or simply "expression vectors". In the present invention, the expression of any nucleic acid sequence is directed by operatively linking the promoter sequences of the invention to the nucleic acid sequence to be expressed. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The vector may also contain additional sequences, such as a polylinker for subcloning of additional nucleic acid sequences and a polyadenylation signal to effect proper polyadenylation of the transcript. The nature of the polyadenylation signal is not believed to be crucial to the successful practice of the invention, and any such sequence may be employed, including but not limited to the SV40 and bovine growth hormone poly-A sites. The vector may further include a termination sequence, which can serve to enhance message levels and to minimize read through from the construct into other sequences. Finally, expression vectors typically have selectable markers, often in the form of antibiotic resistance genes, that permit selection of cells that carry these vectors.

In a further embodiment, the present invention provides recombinant host cells in which the expression vectors disclosed herein have been introduced. As used herein, the term "host cell" is intended to refer to a cell into which a nucleic acid of the invention, such as a recombinant expression vector of the invention, has been introduced. Such cells may be prokaryotic or eukaryotic.

The terms "host cell" and "recombinant host cell" are used interchangeably herein. It should be understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The host cells can be transiently or stably transfected with one or more of the expression vectors of the invention. Such transfection of expression vectors into prokaryotic and eukaryotic cells can be accomplished via any technique known in the art, including but not limited to standard bacterial transformations, calcium phosphate co-precipitation, electroporation, or liposome mediated-, DEAE dextran mediated-, polycationic mediated-, or viral mediated transfection. Alternatively, the host cells can be infected with a recombinant viral vector comprising the GIP90/130 nucleic acid. (See, for example, *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press; *Culture of Animal Cells: A Manual of Basic Technique*, 2<sup>nd</sup> Ed (R.I. Freshney. 1987. Liss, Inc. New York, NY).

In a further aspect, the invention provides methods for detecting the presence of the GIP90/130 polypeptides in a protein sample, comprising providing a protein sample to be screened, contacting the protein sample to be screened with an antibody against one or more GIP90/130 polypeptides, and detecting the formation of antibody-GIP90/130 polypeptide complexes. The antibody can be either polyclonal or monoclonal, although monoclonal antibodies are preferred. As used herein, the term "protein sample" refers to any sample that may contain GIP90/130 polypeptides, including but not limited to tissues and portions thereof, tissue sections, intact cells, cell extracts, purified or partially purified protein samples, bodily fluids, and nucleic acid expression libraries. Accordingly, this aspect of the present invention may be used to test for the presence of GIP90/130 polypeptides in these various protein samples by standard techniques including, but not limited to, immunolocalization, immunofluorescence analysis, Western blot analysis, ELISAs, and nucleic acid expression library screening, (See for example, Sambrook et al, 1989.) In one embodiment, the techniques may determine only the presence or absence of GIP90/130 polypeptides. Alternatively, the techniques may be quantitative, and provide information about the relative amount of GIP90/130 polypeptides in the sample. For quantitative purposes, ELISAs are preferred.

Detection of immunocomplex formation between GIP90/130 polypeptides and antibodies or fragments thereof directed against GIP90/130 polypeptides can be accomplished by standard detection techniques. For example, detection of immunocomplexes can be accomplished by using labeled antibodies or secondary  
5 antibodies. Such methods, including the choice of label are known to those ordinarily skilled in the art. (Harlow and Lane, Supra). Alternatively, the polyclonal or monoclonal antibodies can be coupled to a detectable substance. The term "coupled" is used to mean that the detectable substance is physically linked to the antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials,  
10 luminescent materials and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase,  $\beta$ -galactosidase, or acetylcholinesterase. Examples of suitable prosthetic-group complexes include streptavidin/biotin and avidin/biotin. Examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein,  
15 dansyl chloride or phycoerythrin. An example of a luminescent material includes luminol. Examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or  $^3\text{H}$ .

Such methods of detection are useful for a variety of purposes, including but not limited to detecting an autoimmune condition, identifying cell division arrest or cell death, detecting GIP90/130 interactions with GPBP or other proteins,  
20 immunolocalization of GIP90/130 polypeptides in a tissue sample, Western blot analysis, and screening of expression libraries to find related proteins.

In yet another aspect, the invention provides methods for detecting the presence of nucleic acid sequences encoding GIP90/130 polypeptides in a sample comprising providing a nucleic acid sample to be screened, contacting the sample with a nucleic  
25 acid probe derived from the isolated nucleic acid sequences of the invention, or fragments thereof, and detecting complex formation.

As used herein, the term "sample" refers to any sample that may contain a GIP90/130 polypeptide-encoding nucleic acid, including but not limited to tissues and portions thereof, tissue sections, intact cells, cell extracts, purified or partially purified  
30 nucleic acid samples, DNA libraries, and bodily fluids. Accordingly, this aspect of the present invention may be used to test for the presence of GIP90/130 polypeptide-encoding mRNA or DNA in these various samples by standard techniques including, but not limited to, *in situ* hybridization, Northern blotting, Southern blotting, DNA library screening, polymerase chain reaction (PCR) or reverse transcription-PCR (RT-PCR).

(See for example, Sambrook et al, 1989.) In one embodiment, the techniques may determine only the presence or absence of the nucleic acid of interest. Alternatively, the techniques may be quantitative, and provide information about the relative amount of the nucleic acid of interest in the sample. For quantitative purposes, quantitative PCR and RT-PCR are preferred. Thus, in one example, RNA is isolated from a sample, and contacted with an oligonucleotide derived from the GIP90/130 polypeptide-encoding nucleic acid sequence, together with reverse transcriptase, under suitable buffer and temperature conditions to produce cDNAs from the GIP90/130 RNA. The cDNA is then subjected to PCR using primer pairs derived from the appropriate nucleic acid sequence disclosed herein. In a preferred embodiment, the primers are designed to detect the presence of the RNA expression product of GIP90/130, and the amount of GIP90/130 gene expression in the sample is compared to the level in a control sample.

For detecting GIP90/130 nucleic acid sequences, standard labeling techniques can be used to label the probe, the nucleic acid of interest, or the complex between the probe and the nucleic acid of interest, including, but not limited to radio-, enzyme-, chemiluminescent-, or avidin or biotin-labeling techniques, all of which are well known in the art. (See, for example, *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA)).

Such methods of nucleic acid detection are useful for a variety of purposes, including but not limited to detecting an autoimmune condition, identifying cell division arrest or cell death, identifying cells that express GIP90/130 nucleic acid sequences, in situ hybridization for GIP90/130 gene expression, Northern and Southern blot analysis, and DNA library screening.

As discussed above, GIP90/130 polypeptides are likely to be involved in cell signaling pathways that impair cell division or cause cell death, which are thought to be up-regulated during autoimmune pathogenesis and down-regulated in cancer cells to prevent autoimmune attack during tumor growth. Thus, the detection methods disclosed herein can be used to detect cells that are undergoing such cell death-related processes.

Furthermore, the present invention provides method for treating an autoimmune disorder or cancer comprising modifying the expression or activity of GIP90/130 RNA

or GIP90/130 polypeptides, such as by increasing or decreasing their expression or activity. Modifying the expression or activity of GIP90/130 RNA or GIP90/130 polypeptides can be accomplished by using specific inducers or inhibitors of GIP90/130 polypeptide expression or activity, such as GIP90/130 antibodies, polypeptides  
5 representing interactive motifs of GIP90/130 such as those disclosed herein, antisense or RNA interference therapy based on the design of antisense oligonucleotides or double stranded RNAs to the GIP90/130 nucleic acid sequences disclosed herein, cell therapy using host cells expressing one or more GIP90/130 polypeptides, or other techniques known in the art. As used herein, "modification of expression or activity" refers to  
10 modifying expression or activity of either the RNA or protein product.

For example, knowing that the GIP90/130 gene is a tumor suppressor gene, that aberrantly increased cell death processes are the basis of specific autoimmune pathogenesis (WO 00/50607), and that aggregates of GIP90/130 polypeptides are expressed in a number of human tissues that are common target of autoimmune  
15 responses, the administration of GIP90/130 polypeptides or nucleic acids of the invention, particularly those representing essential interactive motifs for GIP90/130 polypeptide aggregation and/or interaction with other cellular components, such as GPBP, would impact pathogenesis and therefore serve as therapeutic agents for autoimmunity. Alternatively, tumor cells express little or no GPBP or GIP90/130, and  
20 thus the administration of the GIP90/130 polypeptide or nucleic acid sequences of the invention, particularly the full length GIP90, GIP130a, GIP130b, and/or GIP130c, alone or in combination with GPBP, is expected to provide a therapeutic benefit in patients with cancer.

While not being limited to any specific mechanism of action, it is believed that a  
25 therapeutic benefit in cancer patients would be derived by promoting GIP90/130 interactions with other cellular constituents, such as GPBP and/or GIP90/130 aggregation, whereas a therapeutic benefit to autoimmunity patients would be derived by inhibiting these interactions and/or aggregation.

In another aspect, the invention provides methods for modifying GIP90/130  
30 activity comprising contacting cells with an amount effective of one or more of the polypeptides, antibodies, nucleic acids, or pharmaceutical compositions thereof, of the invention to modify GIP90/130 activity. Such cell contacting can be in vitro or in vivo, and "modifying" includes both increasing or decreasing GIP90/130 activity, including transcription-promoting activity.

In another aspect, the invention provides methods for modifying GPBP activity, comprising contacting cells with an amount effective of one or more of the polypeptides, antibodies, nucleic acids, or pharmaceutical compositions thereof, of the invention to modify GPBP activity. Such cell contacting can be in vitro or in vivo, and  
5 “modifying” includes both increasing or decreasing GPBP activity. For example, augmented GPBP activity is associated with autoimmunity, and thus the administration of the GIP90/130 polypeptides or antibodies of the invention (or gene therapy by administration of the GIP90/130 nucleic acid sequences or vectors thereof of the invention) would be expected to impact GPBP-GIP90/130 interactions, and to provide a  
10 therapeutic benefit in patients with an autoimmune disorder. Alternatively, tumor cells express little or no GPBP, and thus the co-administration of the GIP90/130 polypeptides of the invention, particularly the full length GIP90, GIP130a, GIP130b, and/or GIP130c, in combination with GPBP, would be expected to provide a therapeutic benefit in patients with cancer.

15 In another aspect, the present invention provides methods for modifying pol  $\kappa$ 76 polypeptide activity, comprising contacting cells with an amount effective of one or more of the polypeptides, antibodies, nucleic acids, or pharmaceutical compositions thereof, of the invention to modify pol  $\kappa$ 76 activity. Such cell contacting can be in vitro or in vivo, and “modifying” includes both increasing or decreasing pol  $\kappa$ 76 activity. For  
20 example, augmented pol  $\kappa$ 76 activity is associated with autoimmunity (WO 02/46378), and thus the administration of the GIP90/130 polypeptides or antibodies of the invention (or gene therapy by administration of the GIP90/130 nucleic acid sequences or vectors thereof of the invention) would be expected to impact pol  $\kappa$ 76-GIP90/130 interactions, and to provide a therapeutic benefit in patients with an autoimmune disorder.

25 In practicing the therapeutic methods of the invention, the amount or dosage range of the GIP90/130 polypeptides or antibodies thereto generally ranges between about 0.01  $\mu$ g/kg body weight and about 10 mg/kg body weight, preferably ranging between about 0.10  $\mu$ g/kg and about 5 mg/kg body weight, and more preferably between about 1  $\mu$ g/kg and about 5 mg/kg body weight.

30 In a further aspect, the present invention provides pharmaceutical compositions, comprising an amount effective of the GIP90/130 polypeptides, antibodies thereto, and nucleic acids disclosed herein to carry out one or more of the therapeutic methods of the invention, and a pharmaceutically acceptable carrier. The GIP90/130 polypeptides, or

antibodies thereto, may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc.

For administration, the polypeptides are ordinarily combined with one or more  
5 adjuvants appropriate for the indicated route of administration. The compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and tableted or encapsulated for conventional administration.  
10 Alternatively, the compounds of this invention may be dissolved in saline, water, polyethylene glycol, propylene glycol, carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art. The carrier or diluent may include time delay material, such as  
15 glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art.

The polypeptides or pharmaceutical compositions thereof may be administered by any suitable route, including orally, parentally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional pharmaceutically acceptable  
20 carriers, adjuvants, and vehicles. The term parenteral as used herein includes, subcutaneous, intravenous, intra-arterial, intramuscular, intrasternal, intratendinous, intraspinal, intracranial, intrathoracic, infusion techniques or intraperitoneally. In preferred embodiments, the polypeptides are administered intravenously or subcutaneously.

25 The polypeptides may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (e.g., solutions, suspensions, or emulsions). The polypeptides of the invention may be applied in a variety of solutions. Suitable solutions for use in accordance with the invention are sterile, dissolve sufficient amounts of the polypeptides, and are not harmful for the proposed application.

30 The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

## Examples

### *Identification and Characterization of GIP90/130 polypeptides*

We performed a yeast two-hybrid screening on several human cDNA libraries searching for GPBP-interactive proteins. The screenings were performed using full length GPBP as bait, cloned in vector pGBT9 to generate the GAL4 binding domain-  
5 fusion protein. With the resulting construct we transformed yeast HF7c cells to obtain a stably transfected cell line which was subsequently transformed with the different cDNA libraries we have used: Human Skeletal Muscle (pGAD10 vector), Human Kidney (pGAD10), Human Pancreas (pGAD10), Human Brain (pACT2) and Hela  
10 (pGADGH) cDNA libraries (all from Clontech). The transformations were carried out according to the supplier's instructions and plated on medium deficient in Trp, Leu and His containing 20 mM 3-amino-1,2,4-triazol. Interactions were assessed following the manufacture's recommendations. Specifically  $\beta$ -galactosidase activity was assayed with X-GAL (0.75 mg/ml) for the lift colony assays and with ortho-nitrophenyl  $\beta$ -D  
15 galactopyranoside (0.66 mg/ml) for the in-solution determinations.

We isolated an 800 bp cDNA ("I-20 cDNA") encompassing an open reading frame (ORF) which encodes a 265 residue polypeptide, I-20 (SEQ ID NO:6); from a human skeletal muscle library. Part of the ORF coincided with the ORF encoding DOC1 (down-regulated in ovarian cancer 1) (GenBank accession NP\_055705) (Mok et  
20 al., Gynecol. Oncol. 52(2):247-252 (1994)), a polypeptide whose encoding mRNA is not found in ovarian cancer cell lines, but is abundantly expressed in normal ovarian cell lines. For this reason, the DOC-1 gene is considered to be a tumor suppressor gene.

Using the I-20 cDNA, we probed a multi-tissue Northern blot (Clontech) to determine the level of expression of the I-20 encoding mRNA in normal human tissues  
25 and in a number of human cancer cell lines. The membranes were hybridized with  $^{32}\text{P}$ - $\alpha$ -dCTP labelled I-20 cDNA (SEQ ID NO:5), and specific mRNAs species were identified by autoradiography. We identified four mRNA species of 9, 4.4, 4 and 3 Kb. The species of 9, 4.4 and 3 Kb were more abundant in skeletal muscle, while the 4 Kb species displayed similar expression in skeletal muscle, pancreas and lung, and higher  
30 expression in heart tissue. With the exception of heart, which contained traces of the 9, 4.4 and 3 Kb species, the rest of the tissues tested mainly expressed the 4 Kb mRNA species. As expected from previous studies for DOC1, I-20 cDNA did not hybridize significantly to any mRNA species from the individual human cancer cell lines tested



(MTN human cancer cell line blot from Clontech), thus confirming I-20 as being encoded by a tumor suppressor gene.

Since the I-20 ORF contained no stop codon and extended 5' past the ORF proposed for DOC1, we explored the possibility that in skeletal muscle I-20 represents a partial sequence of a larger protein. By probing the corresponding cDNA library with the I-20 cDNA, we isolated and characterized by nucleotide sequencing four overlapping cDNA clones which in total comprise an ORF encoding a predicted 764-amino acid polypeptide of 90 kDa that was named GIP90 (SEQ ID NO:10), for GPBP interacting protein 90 kDa. The existence of GIP90 mRNA was confirmed by isolating and nucleotide sequencing a continuous PCR fragment derived from the same library containing the proposed overlapping ORF. The more remarkable structural features of GIP90 are the presence of two nuclear localization signals (NLS), one in the N terminal region and another at the C terminal region, and a highly predictable coiled-coil formation through most of its sequence including two leucine zippers.

Using the cDNA nucleotide sequence of GIP90 ("GIP90 cDNA") (SEQ ID NO: 9) we carried out a BLAST search against the human genome and found that GIP90 cDNA matched at chromosome 3 (3q12) (genomic DNA accession numbers NT\_030634 for exon I and NT\_033050 for the rest of the exons). We determined the exon/intron structure for the GIP90 genomic sequence, which encompass a total of six exons (Figure 1). Exons I-IV of the GIP90 gene contain 5' untranslatable sequence and encode the first 201 residues of an N-terminal segment of 240 residues that is absent in DOC1 and DOC1-related protein (GenBank accession number AAH27860). Exon V encodes the remaining 39 residues not present in DOC proteins as well as the additional 524-residues of GIP90, and exon VI contains 3' untranslatable sequence.

Comparison of the GIP90 cDNA and the GIP90 genomic sequence revealed the existence of an adenine (A) at position 2720 ( $A^{2720}$ ) in the GIP90 cDNA that was not present in the GIP90 genomic DNA, suggesting that GIP90 cDNA represents either a cDNA artifact, or a native mRNA species that derives from a DNA polymorphism or mRNA editing. Mutational artifacts are generally unique events unlikely to be found in more than one cDNA molecular species. We have identified  $A^{2720}$  in at least two different GIP90 cDNA fragments, representing two different reverse transcription events, and PCR on total cDNA from the human muscle library (Clontech) using a forward primer from exon I and a reverse primer from exon VI, and subsequent direct sequencing, revealed that the resulting cDNA exclusively contained  $A^{2720}$ . A

homologous nucleotide was also found in a DOC1 encoding sequence, but not in DOC1-related protein encoding sequences. These results indicate that the A<sup>2720</sup> in the GIP90 cDNA does not represent an artifact.

In order to further analyze the origin of GIP90 cDNA, we studied the expression  
5 of GIP90 in two independent human skeletal muscle tissue samples by RT-PCR. We were unable to amplify GIP90 mRNA from these samples. In contrast, we isolated and characterized a continuous cDNA fragment (SEQ ID NO:11) representing a related mRNA species that encodes a 130 kDa polypeptide (1135-residues) that we named GIP130a (SEQ ID NO:12). GIP130a results from faithful transcription and translation  
10 of the GIP90 genomic sequence (ie: no A<sup>2720</sup>), suggesting that a specific mechanism for mRNA diversification is responsible for the production of GIP90 encoding mRNA from the GIP90 genomic sequence.

To further explore the mRNA diversification mechanism of the DOC1/GIP90/130 family, we compared the nucleotide sequences encoding  
15 DOC1/DOC1-related protein, GIP90, and GIP130a. Several nucleotide differences were identified, namely: (1) DOC-1 and DOC1-related mRNA are devoid of exon I-IV; (2) DOC1 mRNA showed nucleotide deletions of 42- and 18-bp in exon V, and both DOC1 and DOC1-related mRNA contain an additional 276-bp at the 3' end of this exon, which corresponds to an intron sequence in GIP90/130a; (3) DOC-1 and DOC1-related  
20 mRNAs are both devoid of exon VI.

Therefore, it appeared that the expression of exon VI is associated with expression of GIP90/130a mRNAs, and that DOC-1 and DOC1-related mRNAs are exclusively encoded by an intron-extended exon V. The existence of DOC-1 mRNAs containing exons I-IV was then assessed by PCR of mRNA from human skeletal muscle  
25 and from human 293 cells. We obtained two different cDNAs (SEQ ID NOS: 13 and 15) both containing exon I-V sequences and DOC-1 exclusive exon V, and diverging with respect to each other in one single nucleotide (A/G) at position 975, which leads to an amino acid change at position 168 (H<sup>168</sup>/R<sup>168</sup>). This results in two different 1133-residue long polypeptides (130-kDa) which we named GIP130b (SEQ ID NO: 14) and  
30 GIP130c (SEQ ID NO: 16), respectively. A comparison of the amino acid sequences of GP90/130 polypeptides and the DOC1 polypeptide family is shown in Figure 3.

The amino acid sequence of rat filamin A-interacting protein (FILIP) (Genbank accession number BAC00851) and hypothetical human KIAA1275 protein (Genbank accession number BAA86589) are highly homologous (approximately 50%) to the

GIP90/130 and DOC proteins. This suggests that these genes are related and that FILIP, KIAA1275 and GIP90/130 are likely to share biological functions. Therefore, knowing that FILIP impairs cell migration of cortical neurons (Nature Cell Biology 2002 Jul;4(7):495-501), it is plausible to hypothesize that GIP90/130 polypeptides exert their tumor suppressor activity, at least in part, by impairing cell migration.

The above data demonstrate that the DOC-1/GIP90/130 mRNA family results from a complex diversification mechanism operating on the expression of the corresponding gene (GIP90 genomic sequence). Thus, we have found that the presence of R<sup>168</sup> or H<sup>168</sup> is the result of a GIP90 genomic sequence polymorphism. The presence of exon V, which is characteristic of GIP90/GIP130a (exon Va), is linked to the expression of exon VI and represents a complex alternative exon splicing in which the alternative use of two 5' splice sites of an intron is coordinated with the splicing of an alternative 3' terminal exon. Thus, when the more upstream 5' splice site is used to yield a shorter exon V (exon Va), the 3' terminal exon (exon VI) is spliced, whereas when using the more downstream 5' splice site resulting in a larger exon V (exon Vb), the 3' terminal exon (exon VI) is not spliced. Regarding A<sup>2720</sup>, we still are in the process of determining the specific diversification mechanism responsible for its presence. The exon/ intron structure of the gene for the DOC-1/GIP90/130 family is shown in Figure 1 and a scheme for the more relevant features regarding mRNA and protein structure for the GIP family is presented in Figure 2. Finally, similar genetic diversification mechanisms perhaps are responsible for the deletion of C<sup>2708</sup> in DOC1 and an aberrant alternative splicing within long exons (previously described for other genes) appears to account for the 42- and 18- bp deletions found in DOC1 mRNA.

The presence of R<sup>168</sup> in GIP90 generates a putative bipartite NLS signal and a consensus for PKA phosphorylation, whereas the presence of A<sup>2720</sup> causes a frame-shift in the ORF encoding GIP90, which results in the appearance of a second nuclear localization signal and a premature stop codon. The latter removes a total of 386 residues of the C terminal region that is present in GIP130 proteins. These residues appear to conform to a domain with no predictable coiled-coils containing a number of putative O-glycosylation sites (Figure 2).

#### *Characterization of GIP90/130 interactions*

Using a yeast two-hybrid system, we found that the four members of the GIP90/130 interact with GPBP, although to a more limited extent than I-20 (SEQ ID

NO:6). GIP90 displayed the strongest interaction with GPBP, whereas individual GIP130 proteins interacted similarly with GPBP, although to a lesser extent than GIP90. These data implicate the C-terminal residues of the GIP130 proteins, which are not present in GIP90, and also the C-terminal residues of GIP90 not present in I-20 in a negative modulation of the interaction of GIP90/130 polypeptides with GPBP. Deletion of the N terminal 240-residues of GIP90, GIP130b, and GIP130c resulted in molecular species that do not interact with GPBP, indicating that the N-terminal region contains residues involved in the interaction of GIP90/130 polypeptides with GPBP. All of these findings account for the observation that I-20 (SEQ ID NO: 6), which contains the bulk of this N terminal region (residues 86-240), and does not harbor the inhibitory C terminal regions, displayed the strongest interaction in a two hybrid system with GPBP. The production of additional I-20 deletion mutants and their use in specific two hybrid studies permitted the identification of two specific regions of I-20 that are essential for GPBP interaction as well as the identification of other residues directly involved but not essential for the interaction (Figure 4).

GIP90/130 polypeptides self-aggregate and aggregate with each other in a yeast two-hybrid assays, indicating that, similarly to GPBP (WO 00/50607), GIP90/130 polypeptides aggregate to form homo and hetero oligomers. No significant differences were found among GIP90/130 full length polypeptides in their ability to self-aggregate. Deletion of the N-terminal 240-residues from GIP130b/c results in DOC1-related protein, which aggregates more efficiently and does not interact with GPBP. Since the deleted residues contain motifs for I-20 self-aggregation, it is conceivable that the deleted region contains residues that are critical for GIP90/130 aggregation, but not for DOC/DOC1-related protein aggregation, and that GIP90/130 polypeptides and DOC1 polypeptides aggregate in a different manner. Since the N terminal 240 residues also contain essential residues for GIP90/130 polypeptide interactions with GPBP, this further suggests that GPBP interaction negatively modulates GIP90/130 polypeptide aggregation but not DOC aggregation. Consistently, two hybrid assays using I-20 deletion mutants show that essential sequences for GIP90/130 interactions with GPBP and for I-20 aggregation overlap extensively (Figure 4), strongly suggesting that GPBP binding to GIP90/130 polypeptides prevents GIP90/130 polypeptide aggregation but not DOC aggregation. Accordingly, we have observed with a yeast three-hybrid system that GPBP expression efficiently impairs both I-20 and GIP90 aggregation, and that I-20 and GIP90 efficiently impair GPBP aggregation.

Deletion mutants were obtained using specific primers and PCR, followed by cloning of the resulting cDNAs in the pGBT9 and pGAD424 vectors. The assays were performed in SFY526 or HF7c *Saccharomyces cerevisiae* strains, with pGBT9 as GAL4 binding domain vector and pGAD424 as GAL4 activation domain vector, by the lift colony assay procedure. Briefly, the yeast cells were co-transformed with constructs of both binding domain and activation domain vectors, and the co-transformants were selected in medium deficient in both tryptophan and leucine. After five days of incubation at 30° C the colonies were tested for the expression of  $\beta$ -galactosidase with X-Gal substrate (0.75 mg/ml). The intensity of the blue color displayed in the assay informed us about the relative strength of the interactions. When the assays were performed with the HF7c strain, the interactions were assessed by the lift colony assay procedure and by growth in medium deficient in histidine, tryptophan and leucine. For yeast three-hybrid system, we used the pBRIDGE vector, which allows the conditional expression of a third protein apart from the usual GAL4 binding and activation domain-fusion proteins of the two-hybrid system. In this case, the expression of GPBP or I-20 or GIP90 was driven by Met25 promoter, active in absence of methionine. In these experiments, the transformed SFY526 cells were plated in medium deficient in tryptophan, leucine and methionine, and subjected to the colony lift assay after five days at 30°C. In the case of the strain HF7c the colonies grown in the cited plates were streaked on medium with the additional deficiency of histidine.

In an attempt to establish the viability of these molecular interactions in human cells, the interaction between GIP90 and GPBP was assessed in a mammalian two-hybrid system using 293 cells. We used the CLONTECH mammalian two hybrid kit, with vectors pM and pRK5-GAL4BD as GAL4 binding domain vectors and pVP16 as activation domain vector. We transfected 293 cells by the calcium phosphate procedure with the appropriate constructs and reporter vectors and the interactions determined by the CAT ELISA kit (Roche), following the manufacturer's instructions.

Finally, using a yeast two hybrid system, we investigated the interactions between pol  $\kappa$ /pol  $\kappa$ 76 and GPBP/GPBPA26 and we got no positive results. However, when we challenged interaction between pol  $\kappa$  or pol  $\kappa$ 76 and I-20, we obtained positive results with pol  $\kappa$ 76 but not with pol  $\kappa$ . The positive interaction of I-20 with pol  $\kappa$ 76 suggests that GIP90 is a biological bridge between GPBP and pol  $\kappa$ 76 and that the three

proteins are partners in specific strategies which become deregulated during autoimmune pathogenesis.

From all these data, we conclude that: (1) GIP90/130 polypeptides aggregate in a different manner than DOC/DOC1-related polypeptides; (2) GPBP interacts with GIP90/130 polypeptides and this interaction counteracts GIP90/130 polypeptide aggregation; (3) GPBP does not interact with DOC/DOC1-related proteins, and therefore GPBP is not expected to influence DOC/DOC1-related protein aggregation; (4) I-20 contains essential amino acid sequences involved in GPBP interaction with GIP90/130 polypeptides and in GIP90/130 polypeptide aggregation; (5) the C terminal domain of GIP130 species exerts a negative effect on their interactions with GPBP, and (6) GIP90/130 polypeptides contain sequences not present in I-20 that negatively modulate both GIP90/130 polypeptide interaction with GPBP and GIP90/130 polypeptide aggregation.

#### *Further characterization of GIP90/130*

Given that GPBP is a protein kinase, we assessed the capacity of GPBP to phosphorylate GIP90 in vitro by using purified yeast recombinant counterparts. GIP90 was cloned in pHIL-D2 vector in frame with the FLAG tag at N-terminal position and with a 6 histidine tail at C-terminal position. It was expressed in the *Pichia pastoris* expression system (Invitrogen) and purified with an affinity resin (Clontech) making profit of the polyhistidine tail, using an 8 M urea-containing breaking buffer, which was eliminated by dialysis against Tris-buffered saline. The purified protein was incubated with yeast recombinant GPBP in a suitable reaction buffer and labelled for 12 hours at 30° C. The phosphorylation mixtures were analysed by Western blot using FLAG-specific antibodies (Sigma) and autoradiography. Incubation of purified GIP90 and GPBP in the presence of [ $\gamma^{32}\text{P}$ ] ATP resulted in  $^{32}\text{P}$  incorporation into GIP90, thus confirming that GPBP interacts with GIP90 and phosphorylates it.

Remarkable structural features of GIP90/130 proteins are (1) the existence of two nuclear localization sequences (NLS) whose presence appears to be regulated by single nucleotide replacement or addition (see above); and (2) the existence of a large number of predictable coiled-coil motifs including two leucine zippers. Consequently we have assayed the ability of GIP90/130 and DOC1-related protein to induce transcription from a heterologous promoter of a reporter gene. This was accomplished

by fusing either GIP90, GIP130a, GIP130b or DOC1-related protein to the binding domain of GAL4 transcription factor in a high level expression pAS2-1 vector (Clontech) and transforming SFY526 yeast cells carrying a LacZ reporter gene under the control of a promoter with a GAL4 binding site. Transformants were selected in  
5 tryptophan-deficient medium at 30°C for five days and colony lift assays performed. The GIP90, GIP130a, and GIP130b fusion polypeptides, but not DOC1-related protein fusion polypeptides, efficiently induced expression of LacZ, as estimated by the appearance of  $\beta$ -galactosidase activity.

We have also expressed GIP90 in bacteria, and have used the corresponding  
10 recombinant protein to immunize both rabbits and mice to obtain respectively polyclonal and monoclonal antibodies specific for GIP proteins. GIP90 was cloned in pGEX vector, in frame with glutathione-S-transferase cDNA. The resulting construct was used to transform DH5 $\alpha$  cells and expression of the GST-GIP90 fusion protein was induced with IPTG and further purified on glutathione affinity column. GST-GIP90  
15 purified protein was used to immunize both rabbits and mice in order to obtain respectively polyclonal and monoclonal antibodies. These antibodies were used to identify a native protein in 293 cells displaying the same mobility as recombinant GIP130 which likely represents endogenous GIP130b or GIP130c, since exon VI appears to not be expressed in these cells, as determined by specific RT-PCR  
20 approaches. One of the monoclonal antibodies (Mab3) maps in the N terminal 240 residues of GIP90, whereas Mab 8 maps within the next 509 residues (i.e.: between residues 241-750).

By indirect immunofluorescence on COS-7 cells transiently expressing recombinant GIP90 we have identified cells that expressed GIP90 in the nucleus, cells  
25 expressing GIP90 in the cytosol, and cells that expressed GIP90 in both the nucleus and the cytosol. When these cells co-expressed recombinant GIP90 and GPBP, double indirect immunofluorescence revealed expression of the two proteins at the cytosol and in some cells GIP90 was also detected in the nucleus. We have not seen GIP90 and GPBP being co-expressed in the nucleus. Finally, using confocal microscopy and  
30 NIH3T3 or 293 cells, we have confirmed nuclear localization of GIP90 and cytosolic co-localization GIP90/GPBP. These cells do not express detectable levels of GIP90/130 polypeptides, as no significant fluorescence was detected when non-transfected cells were incubated with anti-GIP antibodies and an appropriate secondary antibody. For immunofluorescence and confocal microscopy studies, GIP90 cDNA was cloned in

pRK5 mammalian expression vector, and this construct was used alone or co-transfected with GPBP cloned in pCDNA3 vector (Invitrogen), using the DEAE-dextran or calcium phosphate procedures. After 24 hours of incubation at 37°C, the cells were washed with phosphate-buffered saline (PBS), fixed with methanol or methanol:acetone, blocked with 3% BSA in PBS and incubated with a pool of mouse anti-GIP90 monoclonal antibodies and rabbit anti-GPBP polyclonal antibodies. FITC-conjugated anti-mouse IgG and TRITC-conjugated anti-rabbit IgG antibodies were respectively used as secondary antibody.

Finally, we have performed immunohistochemistry studies on paraffin embedded human tissues and have found GIP proteins to localize in a number of cells and structures also expressing GPBP. Immunohistochemistry studies were done on human multi-tissue control slides (Biomed, Dako), using the ABC peroxidase method. GIP proteins are widely expressed in human tissues, but are more abundantly expressed in some locations. A strong staining is found in smooth muscle cells, particularly in those of vessel walls, with a diffuse cytoplasmic pattern. There is intense expression in alveolar septa, with a linear pattern suggestive of being associated to basement membrane locations, along with cytoplasmic staining of the pneumocytes. The kidneys show expression in the epithelial cells of the tubules, mainly in distant ones, and also in mesangial cells and podocytes of the glomerulus. In the pancreas there is staining in the cells of endocrine Langerhans islets. In the adrenal gland, the cortical cells show higher expression than the medullar cells. In the liver, hepatocytes show expression of the GIP90/130, which is higher at the epithelial cells of the biliary ducts. The white matter of the central nervous system shows diffuse staining with a fibrillar pattern, with presence also found in some neuronal bodies. Expression of the GIP90/130 is also evident at the epithelial cells of the prostate, breast, bronchi and intestine, in striated muscle cells of the myocardium, in secretory cells of the pituitary, and in spermatogonium and Leydig cells in the testicle.

The expression of the GIP90/130 is quite similar to that previously described for GPBP (WO 00/50607), with staining in tissues targeted by autoimmune responses, such as the Langerhans islets (type I diabetes), the white matter of the central nervous system (multiple sclerosis), the biliary ducts (primary biliary cirrhosis), the cortex of the adrenal gland (Addison disease), alveolar septa (Goodpasture syndrome), and spermatogonium (male infertility).



The evidence suggests that GIP90/130 is a family of proteins encoded by a tumor suppressor gene, which display transcription factor activity, and which interact and are phosphorylated by GPBP. Given the role of GPBP in autoimmune pathogenesis and in cancer, GIP90/130 represent a potential therapeutic or therapeutic target in these disorders.

5

We claim:

1. An isolated polypeptide comprising at least 6 amino acids of the amino acid of SEQ ID NO:2.
2. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:2.
3. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:4.
4. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:6.
5. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:8.
6. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:10.
7. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:12.
8. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:14.
9. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:16.
10. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:32.
11. The isolated polypeptide of claim 1 comprising the amino acid sequence of SEQ ID NO:36.
12. The isolated polypeptide of claim 1 consisting of at least 6 amino acids of the amino acid sequence of SEQ ID NO:2.
13. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:2.
14. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:4.
15. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:6.
16. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:8.

17. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:10.
18. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:12.
- 5 19. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:14.
20. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:16.
21. The isolated polypeptide of claim 1 consisting of the amino acid sequence of  
10 SEQ ID NO:32.
22. The isolated polypeptide of claim 1 consisting of the amino acid sequence of SEQ ID NO:36.
23. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:34.
24. The isolated polypeptide of claim 23 wherein the polypeptide consists of the  
15 amino acid sequence of SEQ ID NO:34.
25. An isolated polypeptide comprising at least 8 amino acids of the amino acid sequence of SEQ ID NO:18.
26. The isolated polypeptide of claim 25 wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:18.
- 20 27. The isolated polypeptide of claim 25 wherein the polypeptide consists of at least 8 amino acids of the amino acid sequence of SEQ ID NO:18.
28. The isolated polypeptide of claim 25 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:18.
29. An isolated polypeptide consisting of at least 8 amino acids of the amino acid of  
25 SEQ ID NO:20.
30. The isolated polypeptide of claim 29 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:20.
31. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:22.
32. The isolated polypeptide of claim 31 wherein the polypeptide consists of the  
30 amino acid sequence of SEQ ID NO:22.
33. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:24.
34. The isolated polypeptide of claim 33 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:24.
35. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:26.

36. The isolated polypeptide of claim 35 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:26.
37. An isolated polypeptide comprising at least 6 amino acids of the amino acid sequence of SEQ ID NO:28.
- 5 38. The isolated polypeptide of claim 37 wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:28.
39. The isolated polypeptide of claim 37 wherein the polypeptide consists of at least 6 amino acids of the amino acid sequence of SEQ ID NO:28.
40. The isolated polypeptide of claim 37 wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:28.
- 10 41. An isolated polypeptide consisting of at least 6 amino acids of the amino acid sequence of SEQ ID NO:30.
42. The isolated polypeptide of claim 41 wherein the polypeptide consist of the sequence of SEQ ID NO:30.
- 15 43. An isolated polypeptide consisting of the amino acid sequence of SEQ ID NO:38.
44. An antibody directed against a polypeptide comprising an amino acid sequence of one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:32, and SEQ ID NO:36.
- 20 45. The antibody of claim 44 wherein the antibody is directed against a polypeptide comprising an amino acid sequence of one or more of the amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:18, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:32, and SEQ ID NO:36.
- 25 46. An isolated nucleic acid sequence comprising a sequence that hybridizes under high stringency conditions to a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35.
- 30 47. The nucleic acid sequence of claim 46, wherein the isolated nucleic acid sequence comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:17, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35.

48. The isolated nucleic acid sequence of claim 46, wherein the nucleic acid sequence comprises a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:31, and SEQ ID NO:35.
49. The isolated nucleic acid sequence of claim 46, wherein the nucleic acid encodes an amino acid sequence comprising one or more sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:32, and SEQ ID NO:36.
50. An isolated nucleic acid sequence encoding the polypeptide of any one of claims 1-43.
51. A recombinant expression vector comprising the isolated nucleic acid sequence of any one of claims 46-50.
52. A recombinant host cell transfected with the recombinant expression vector of claim 51.
53. A method for detecting a GIP90/130 polypeptide, comprising
- a) providing a protein sample to be screened;
  - b) contacting the protein sample to be screened with the antibody of claim 44 or 45 under conditions that promote antibody-GIP90/130 polypeptide complex formation; and
  - c) detecting the formation of antibody-polypeptide complexes, wherein the presence of the antibody-GIP90/130 polypeptide complexes indicates the presence of a GIP90/130 polypeptide in the protein sample.
54. The method of claim 53, wherein detecting comprises a method selected from the group consisting of immunolocalization, immunofluorescence analysis, Western blot analysis, ELISAs, and nucleic acid expression library screening.
55. A method for detecting a GIP90/130 encoding nucleic acid sequence in a sample, comprising
- a) contacting the sample with a probe comprising a nucleic acid sequence according to any one of claims 33-37 under conditions that promote complex formation between the probe and a GIP90/130 encoding nucleic acid in the sample; and

b) detecting complex formation between the probe and the GIP90/130 encoding nucleic acid in the sample.

56. A method for modifying interactions between GPBP and GIP90/130 polypeptides comprising contacting cells with an amount effective of a polypeptide according to any one of claims 1-43 to modify the interaction between GPBP and GIP.

57. A method for modifying aggregation of GIP90/130 polypeptides comprising contacting cells with an amount effective of a polypeptide according to any one of claims 1-43 to modify the aggregation of GIP90/130 polypeptides.

10 58. A method for modifying interaction between GPBP and GIP90/130 polypeptides comprising contacting cells with an amount effective of one or more antibodies directed against a GIP90/130 polypeptide to inhibit the interaction between GPBP and GIP.

59. The method of claim 58 wherein the antibody comprises one or more antibodies according to claim 44 or 45.

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60. A method for modifying aggregation of GIP90/130 polypeptides comprising contacting cells with an amount effective of one or more antibodies directed against a GIP90/130 polypeptide to modify the aggregation of GIP 90/130 polypeptides.

20 61. The method of claim 60 wherein the antibody comprises one or more antibodies according to claim 44 or 45.

62. A method for modifying GIP90/130 polypeptide activity comprising contacting cells with an amount effective of a polypeptide according to any one of claims 1-43 to  
25 modify GIP90/130 polypeptide activity.

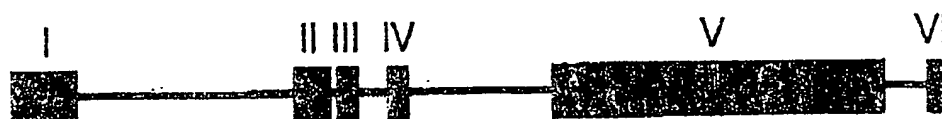
63. A method for modifying GIP90/130 polypeptide activity comprising contacting cells with an amount effective of one or more antibodies directed against a GIP90/130 polypeptide to modify GIP90/130 polypeptide activity.

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64. The method of claim 63 wherein the antibody comprises one or more antibodies according to claim 44 or 45.

65. A pharmaceutical composition comprising:

- a) an isolated polypeptide according to any one of claims 1-43; and
  - b) a pharmaceutically acceptable carrier.
66. A pharmaceutical composition comprising:
- a) an antibody specific for one or more GIP90/130 polypeptides; and
  - b) a pharmaceutically acceptable carrier.
67. A pharmaceutical composition comprising:
- a) an antibody according to claim 44 or 45; and
  - b) a pharmaceutically acceptable carrier.
68. A method for treating a patient with an autoimmune disorder, comprising modifying the expression or activity of one or more GIP90/130 polypeptides in the patient with the autoimmune disorder.
69. A method for treating a patient with a tumor, comprising modifying the expression or activity of one or more GIP90/130 polypeptides in the patient with the tumor.
70. A method for modifying interactions between pol k76 and GIP90/130 polypeptides comprising contacting cells with an amount effective of a polypeptide according to any one of claims 1-43 to modify the interaction between pol k76 and GIP.
71. A method for modifying interaction between pol k76 and GIP90/130 polypeptides comprising contacting cells with an amount effective of one or more antibodies directed against a GIP90/130 polypeptide to inhibit the interaction between pol k76 and GIP90/130 polypeptides.
72. The method of claim 71 wherein the antibody comprises one or more antibodies according to claim 44 or 45.



EXON	SIZE	INTRON	SIZE
I	462 bp	I	162 kb
II	262 bp	II	0.9 kb
III	173 bp	III	5.4 kb
IV	179 bp	IV	73.2 kb
V	3056 bp	V	14.8 kb
VI	118 bp		

FIGURE 1



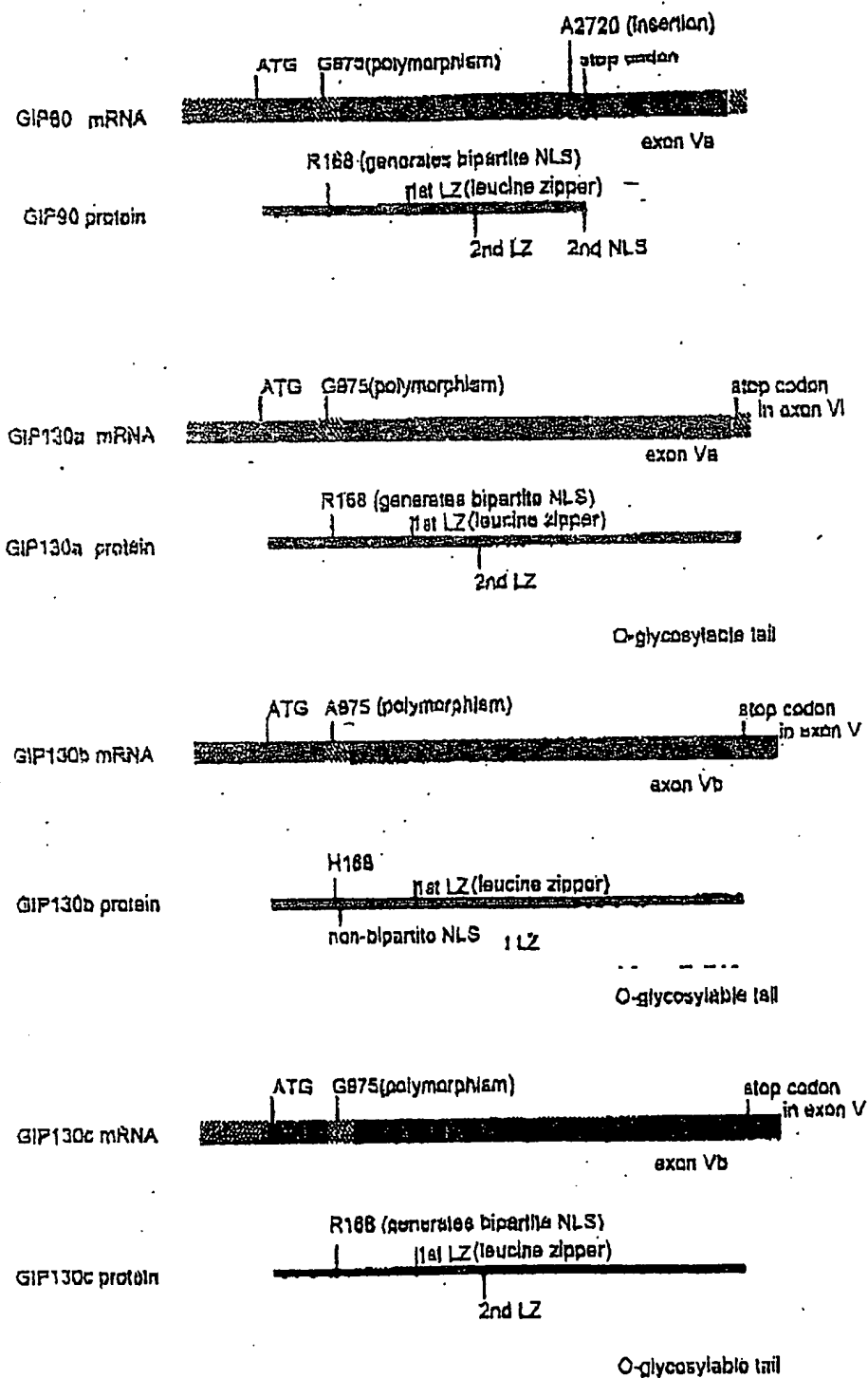


FIGURE 2

FIGURE 3

GIP90 MRSRGSDEGSAQKKFPRHTKGHSFQGPKNMKHRQODKDSFSESDVILPCPKAEKPHSGN  
GIP130a MRSRGSDEGSAQKKFPRHTKGHSFQGPKNMKHRQODKDSFSESDVILPCPKAEKPHSGN  
GIP130b MRSRGSDEGSAQKKFPRHTKGHSFQGPKNMKHRQODKDSFSESDVILPCPKAEKPHSGN  
GIP130c MRSRGSDEGSAQKKFPRHTKGHSFQGPKNMKHRQODKDSFSESDVILPCPKAEKPHSGN  
SDOC1 -----  
DOC1 -----

GIP90 GHQAEDLSRDDLLFLLSIILEGELQARDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQ  
GIP130a GHQAEDLSRDDLLFLLSIILEGELQARDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQ  
GIP130b GHQAEDLSRDDLLFLLSIILEGELQARDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQ  
GIP130c GHQAEDLSRDDLLFLLSIILEGELQARDEVIGILKAEKMDLALLEAQYGFVTPKKVLEALQ  
SDOC1 -----  
DOC1 -----

GIP90 RDAFQAKSTPWQEDIYEKPMNELDKVVEKHKESYRRI LGQLLVAEKSRROTILELEEKR  
GIP130a RDAFQAKSTPWQEDIYEKPMNELDKVVEKHKESYRRI LGQLLVAEKSRROTILELEEKR  
GIP130b RDAFQAKSTPWQEDIYEKPMNELDKVVEKHKESYRRI LGQLLVAEKSRROTILELEEKR  
GIP130c RDAFQAKSTPWQEDIYEKPMNELDKVVEKHKESYRRI LGQLLVAEKSRROTILELEEKR  
SDOC1 -----  
DOC1 -----

GIP90 KHKEYMEKSDEFICLLEQECERLKKLIDQEI KSQEEKEQEKEKRVTTLKEELTKLKSFAI  
GIP130a KHKEYMEKSDEFICLLEQECERLKKLIDQEI KSQEEKEQEKEKRVTTLKEELTKLKSFAI  
GIP130b KHKEYMEKSDEFICLLEQECERLKKLIDQEI KSQEEKEQEKEKRVTTLKEELTKLKSFAI  
GIP130c KHKEYMEKSDEFICLLEQECERLKKLIDQEI KSQEEKEQEKEKRVTTLKEELTKLKSFAI  
SDOC1 -----  
DOC1 -----

GIP90 MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT  
GIP130a MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT  
GIP130b MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT  
GIP130c MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT  
SDOC1 MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT  
DOC1 MVVDEQQRLTAQLTLQRQKIQELTTNAKETHTKLALAEARVQEEEQKATRLEKELQTQTT  
\*\*\*\*\*

GIP90 KFHQDQDTIMAKLTNEDSQNRQLQOKLAALSQ IDELEETNRS LRKAEELQDIKEKISK  
GIP130a KFHQDQDTIMAKLTNEDSQNRQLQOKLAALSQ IDELEETNRS LRKAEELQDIKEKISK  
GIP130b KFHQDQDTIMAKLTNEDSQNRQLQOKLAALSQ IDELEETNRS LRKAEELQDIKEKISK  
GIP130c KFHQDQDTIMAKLTNEDSQNRQLQOKLAALSQ IDELEETNRS LRKAEELQDIKEKISK  
SDOC1 KFHQDQDTIMAKLTNEDSQNRQLQOKLAALSQ IDELEETNRS LRKAEELQDIKEKISK  
DOC1 KFHQDQDTIMAKLTNEDSQNRQLQOKLAALSQ IDELEETNRS LRKAEELQDIKEKISK  
\*\*\*\*\*

GIP90 GEYGNAGIMAEVEELRKRVLDMEGKDEELI KMEEQCRDLNKRLERETLQSKDFKLEVEKL  
GIP130a GEYGNAGIMAEVEELRKRVLDMEGKDEELI KMEEQCRDLNKRLERETLQSKDFKLEVEKL  
GIP130b GEYGNAGIMAEVEELRKRVLDMEGKDEELI KMEEQCRDLNKRLERETLQSKDFKLEVEKL  
GIP130c GEYGNAGIMAEVEELRKRVLDMEGKDEELI KMEEQCRDLNKRLERETLQSKDFKLEVEKL  
SDOC1 GEYGNAGIMAEVEELRKRVLDMEGKDEELI KMEEQCRDLNKRLERETLQSKDFKLEVEKL  
DOC1 GEYGNAGIMAEVEEL-----I KMEEQCRDLNKRLERETLQSKDFKLEVEKL  
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GIP130a KTEFTLKEDLTCLKLTLMFVDERKTMSEKLKKTEDKLOAASSQLQVEQNKVTTVTEKLI  
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DOC1 KTEFTLKEDLTCLKLTLMFVDERKTMSEKLKKTEDKLOAASSQLQVEQNKVTTVTEKLI  
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GIP90 ALKEKIHEYMATEDI LCHLQGDH SVLQKKTKSTRKQEORFRKRD-----  
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GIP130c TSTEDLMNLEQGMSPIITMATFARAQTPESCGSLTPERTMSPIQVLAVTGSASSPEQGRSP  
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DOC1

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GIP130c ASPSAPLQDNRTQGLINGALNKT TNKV TSSITITPTATPLPRQSQITVSNIN--  
SDOC1 ASPSAPLQDNRTQGLINGALNKT TNKV TSSITITPTATPLPRQSQITVSNIN--  
DOC1

## FIGURE 4

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## SEQUENCE LISTING

<110> Saus, Juan  
Revert-Ros, Francisco

<120> GIPs, a Family of Polypeptides with Transcription Factor Activity that Interact with Goodpasture Antigen Binding Protein

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<151> 2001-12-07

<150> US 60/382,004

<151> 2002-05-20

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aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa gcg aaa tct Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser 115 120 125	384
acc cct tgg cag gag gac atc tat gag aaa cca atg aat gag ttg gac Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp 130 135 140	432
aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg gga cag Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln 145 150 155 160	480
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caa gaa atc aag tct cag gag gag aag gag caa gaa aag gag aaa agg Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg 210 215 220	672
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Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu  
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Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser  
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Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp  
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Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln  
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Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe  
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Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp  
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 Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser Thr Pro Trp Gln Glu  
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 Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp Lys Val Val Glu Lys  
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 Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu Glu Lys Arg Lys  
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Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp Lys Val Val Glu Lys

50

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His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe Ile Cys Leu Leu Glu  
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Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp Gln Glu Ile Lys Ser  
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Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg Val Thr Thr Leu Lys  
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Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala Thr Arg Leu Glu Lys  
195 200 205

Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln Asp Gln Asp Thr Ile  
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Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn Arg Gln Leu Gln Gln  
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 Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala  
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 cgc cag ctt caa caa aag ctg gca gca ctc agc cgg cag att gat gag 1008  
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Gly	Glu	Leu	Gln	Ala	Arg	Asp	Glu	Val	Ile	Gly	Ile	Leu	Lys	Ala	Glu
				85					90					95	
Lys	Met	Asp	Leu	Ala	Leu	Leu	Glu	Ala	Gln	Tyr	Gly	Phe	Val	Thr	Pro
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Glu	Glu	Lys	Arg	Lys	His	Lys	Glu	Tyr	Met	Glu	Lys	Ser	Asp	Glu	Phe
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Ile	Cys	Leu	Leu	Glu	Gln	Glu	Cys	Glu	Arg	Leu	Lys	Lys	Leu	Ile	Asp
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Gln	Gln	Asp	Lys	Asp	Ser	Pro	Ser	Glu	Ser	Asp	Val	Ile	Leu	Pro	Cys	
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Leu	Ser	Arg	Asp	Asp	Leu	Leu	Phe	Leu	Leu	Ser	Ile	Leu	Glu	Gly	Glu	
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Trp	Gln	Glu	Asp	Ile	Tyr	Glu	Lys	Pro	Met	Asn	Glu	Leu	Asp	Lys	Val	
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Val	Glu	Lys	His	Lys	Glu	Ser	Tyr	Arg	Arg	Ile	Leu	Gly	Gln	Leu	Leu	
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Lys	Arg	Lys	His	Lys	Glu	Tyr	Met	Glu	Lys	Ser	Asp	Glu	Phe	Ile	Cys	
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Leu	Leu	Glu	Gln	Glu	Cys	Glu	Arg	Leu	Lys	Lys	Leu	Ile	Asp	Gln	Glu	
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Ile	Lys	Ser	Gln	Glu	Glu	Lys	Glu	Gln	Glu	Lys	Glu	Lys	Arg	Val	Thr	
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cta gag aag gaa ctg caa acg cag acc aca aag ttt cac caa gac caa Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln Asp Gln 295 300 305			1390
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ggt atc atg gct gaa gtg gaa gag ctc agg aaa cgt gtg cta gat atg Gly Ile Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met 370 375 380	1154
gaa ggg aaa gat gaa gag ctc ata aaa atg gag gag cag tgc aga gat Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp 385 390 395	1202
ctc aat aag agg ctt gaa agg gag acg tta cag agt aaa gac ttt aaa Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys 400 405 410	1250
cta gag gtt gaa aaa ctc agt aaa aga att atg gct ctg gaa aag tta Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu 415 420 425 430	1298
gaa gac gct ttc aac aaa agc aaa caa gaa tgc tac tct ctg aaa tgc Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys 435 440 445	1346
aat tta gaa aaa gaa agg atg acc aca aag cag ttg tct caa gaa ctg Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu 450 455 460	1394
gag agt tta aaa gta agg atc aaa gag cta gaa gcc att gaa agt cgg Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg 465 470 475	1442
cta gaa aag aca gaa ttc act cta aaa gag gat tta act aaa ctg aaa	1490

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aca	tta	act	gtg	atg	ttt	gta	gat	gaa	cgg	aaa	aca	atg	agt	gaa	aaa	1538
Thr	Leu	Thr	Val	Met	Phe	Val	Asp	Glu	Arg	Lys	Thr	Met	Ser	Glu	Lys	
495					500					505					510	
tta	aag	aaa	act	gaa	gat	aaa	tta	caa	gct	gct	tct	tct	cag	ctt	caa	1586
Leu	Lys	Lys	Thr	Glu	Asp	Lys	Leu	Gln	Ala	Ala	Ser	Ser	Gln	Leu	Gln	
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Val	Glu	Gln	Asn	Lys	Val	Thr	Thr	Val	Thr	Glu	Lys	Leu	Ile	Glu	Glu	
			530					535					540			
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Thr	Lys	Arg	Ala	Leu	Lys	Ser	Lys	Thr	Asp	Val	Glu	Glu	Lys	Met	Tyr	
		545					550						555			
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Ser	Val	Thr	Lys	Glu	Arg	Asp	Asp	Leu	Lys	Asn	Lys	Leu	Lys	Ala	Glu	
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Glu	Glu	Lys	Gly	Asn	Asp	Leu	Leu	Ser	Arg	Val	Asn	Met	Leu	Lys	Asn	
575					580					585					590	
agg	ctt	caa	tca	ttg	gaa	gca	att	gag	aaa	gat	ttc	cta	aaa	aac	aaa	1826
Arg	Leu	Gln	Ser	Leu	Glu	Ala	Ile	Glu	Lys	Asp	Phe	Leu	Lys	Asn	Lys	
				595						600				605		
tta	aat	caa	gac	tct	ggg	aaa	tcc	aca	aca	gca	tta	cac	caa	gaa	aac	1874
Leu	Asn	Gln	Asp	Ser	Gly	Lys	Ser	Thr	Thr	Ala	Leu	His	Gln	Glu	Asn	
			610					615					620			
aat	aag	att	aag	gag	ctc	tct	caa	gaa	gtg	gaa	aga	ctg	aaa	ctg	aag	1922
Asn	Lys	Ile	Lys	Glu	Leu	Ser	Gln	Glu	Val	Glu	Arg	Leu	Lys	Leu	Lys	
		625					630					635				
cta	aag	gac	atg	aaa	gcc	att	gag	gat	gac	ctc	atg	aaa	aca	gaa	gat	1970
Leu	Lys	Asp	Met	Lys	Ala	Ile	Glu	Asp	Asp	Leu	Met	Lys	Thr	Glu	Asp	
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gaa	tat	gag	act	cta	gaa	cga	agg	tat	gct	aat	gaa	cga	gac	aaa	gct	2018
Glu	Tyr	Glu	Thr	Leu	Glu	Arg	Arg	Tyr	Ala	Asn	Glu	Arg	Asp	Lys	Ala	
655					660					665					670	
caa	ttt	tta	tct	aaa	gag	cta	gaa	cat	gtt	aaa	atg	gaa	ctt	gct	aag	2066
Gln	Phe	Leu	Ser	Lys	Glu	Leu	Glu	His	Val	Lys	Met	Glu	Leu	Ala	Lys	
				675					680					685		
tac	aag	tta	gca	gaa	aag	aca	gag	acc	agc	cat	gaa	caa	tggt	ctt	ttc	2114
Tyr	Lys	Leu	Ala	Glu	Lys	Thr	Glu	Thr	Ser	His	Glu	Gln	Trp	Leu	Phe	
			690					695					700			
aaa	agg	ctt	caa	gaa	gaa	gaa	gct	aag	tca	ggg	cac	ctc	tca	aga	gaa	2162
Lys	Arg	Leu	Gln	Glu	Glu	Glu	Ala	Lys	Ser	Gly	His	Leu	Ser	Arg	Glu	

705	710	715	
gtg gat gca tta aaa gag aaa att cat gaa tac atg gca act gaa gac Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp 720 725 730			2210
cta ata tgt cac ctc cag gga gat cac tca gtc ctg caa aaa aaa cta Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu 735 740 745 750			2258
aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa aac Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn 755 760 765			2306
ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc agg Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg 770 775 780			2354
cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct aaa Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys 785 790 795			2402
gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag agc Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser 800 805 810			2450
ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag gag Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu 815 820 825 830			2498
agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg tcc Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser 835 840 845			2546
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gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag agt Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser 915 920 925			2786
cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg cca Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro 930 935 940			2834

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tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg tcc Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser 960 965 970	2930
cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct tgt Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys 975 980 985 990	2978
ggc tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg gct Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala 995 1000 1005	3026
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cca aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro 1025 1030 1035	3116
gac cgg cag tca tca tgg cag ttt cag cgt tca aac agc aat agc Asp Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser 1040 1045 1050	3161
tca agt gtg ata act act gag gat aat aaa atc cac att cac tta Ser Ser Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu 1055 1060 1065	3206
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act atc aca cca aca gcc aca cct ctt cct cga caa tca caa att Thr Ile Thr Pro Thr Ala Thr Pro Leu Pro Arg Gln Ser Gln Ile 1115 1120 1125	3386
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His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu  
 35 40 45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala  
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Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu  
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Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu  
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Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro  
 100 105 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser  
 115 120 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp  
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Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln  
 145 150 155 160

Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu  
 165 170 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe  
 180 185 190

Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp  
 195 200 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg

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Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln		
245	250	255
Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr		
260	265	270
Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala		
275	280	285
Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln		
290	295	300
Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn		
305	310	315 320
Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu		
325	330	335
Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln		
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Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile		
355	360	365
Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met Glu Gly		
370	375	380
Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp Leu Asn		
385	390	395 400
Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys Leu Glu		
405	410	415
Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu Glu Asp		
420	425	430
Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys Asn Leu		
435	440	445

Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu Glu Ser  
 450 455 460

Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg Leu Glu  
 465 470 475 480

Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys Thr Leu  
 485 490 495

Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys Leu Lys  
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Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln Val Glu  
 515 520 525

Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu Thr Lys  
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Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr Ser Val  
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Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu Glu Glu  
 565 570 575

Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn Arg Leu  
 580 585 590

Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys Leu Asn  
 595 600 605

Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn Asn Lys  
 610 615 620

Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys Leu Lys  
 625 630 635 640

Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp Glu Tyr  
 645 650 655

Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala Gln Phe  
 660 665 670

Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys Tyr Lys  
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- Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe Lys Arg  
 690 695 700

Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu Val Asp  
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Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp Leu Ile  
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Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu Asn Gln  
 740 745 750

Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn Leu Thr  
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Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg Pro Ser  
 770 775 780

Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys Glu Val  
 785 790 795 800

Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser Leu Ile  
 805 810 815

Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu Ser Glu  
 820 825 830

Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser Phe Lys  
 835 840 845

Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp Ile Pro  
 850 855 860

Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met Gln Thr  
 865 870 875 880

Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu Ser His  
 885 890 895



Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His Val Gln  
 900 905 910

Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser Pro His  
 915 920 925

Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro Lys Gln  
 930 935 940

Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys Ser Lys  
 945 950 955 960

Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser Pro Ile  
 965 970 975

Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys Gly Ser  
 980 985 990

Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala Val Thr  
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Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro Thr  
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Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg  
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Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser  
 1040 1045 1050

Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser  
 1055 1060 1065

Pro Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro  
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Ser Ala Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly  
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Ala Leu Asn Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile  
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Lys Lys Phe Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys  
15 20 25

aac atg aag cat aga cag caa gac aaa gac tcc ccc agt gag tcg gat 146  
Asn Met Lys His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp  
30 35 40 45

gta ata ctt ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc 194  
Val Ile Leu Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly  
50 55 60

cac caa gca gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc 242  
His Gln Ala Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser  
65 70 75

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Ile Leu Glu Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu  
80 85 90

aag gct gaa aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt 338  
Lys Ala Glu Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe  
95 100 105

gtc act cca aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa 386  
Val Thr Pro Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln  
110 115 120 125

gcg aaa tct acc cct tgg cag gag gac atc tat gag aaa cca atg aat 434  
Ala Lys Ser Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn

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Glu Leu Asp Lys Val Val Glu Lys His	Lys Glu Ser Tyr Arg Arg Ile		
145	150	155	
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Leu Gly Gln Leu Leu Val Ala Glu Lys Ser His Arg Gln Thr Ile Leu			
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gag ttg gag gaa gaa aag aga aaa cat	aaa gaa tac atg gag aag agt		578
Glu Leu Glu Glu Glu Lys Arg Lys His	Lys Glu Tyr Met Glu Lys Ser		
175	180	185	
gat gaa ttc ata tgc cta cta gaa cag gaa tgt gaa aga tta aag aag			626
Asp Glu Phe Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys			
190	195	200	205
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Leu Ile Asp Gln Glu Ile Lys Ser Gln Glu Lys Glu Gln Glu Lys			
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Phe Ala Leu Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu			
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Thr His Thr Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu			
270	275	280	285
cag aag gca acc aga cta gag aag gaa ctg caa acg cag acc aca aag			914
Gln Lys Ala Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys			
290	295	300	
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Phe His Gln Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp			
305	310	315	
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Ser Gln Asn Arg Gln Leu Gln Lys Leu Ala Ala Leu Ser Arg Gln			
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Ile Asp Glu Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu			
335	340	345	
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Glu Leu Gln Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn			
350	355	360	365

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gat ctc aat aag agg ctt gaa agg gag acg tta cag agt aaa gac ttt Asp Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe 400 405 410	1250
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tta gaa gac gct ttc aac aaa agc aaa caa gaa tgc tac tct ctg aaa Leu Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys 430 435 440 445	1346
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gaa act aaa agg gcg ctc aag tcc aaa acc gat gta gaa gaa aag atg Glu Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met 545 550 555	1682
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gat gaa tat gag act cta gaa cga agg tat gct aat gaa cga gac aaa Asp Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys 655 660 665	2018
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aag tac aag tta gca gaa aag aca gag acc agc cat gaa caa tgg ctt Lys Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu 690 695 700	2114
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gaa gtg gat gca tta aaa gag aaa att cat gaa tac atg gca act gaa Glu Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu 720 725 730	2210
gac cta ata tgt cac ctc cag gga gat cac tca gtc ctg caa aaa aaa Asp Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys 735 740 745	2258
cta aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu 750 755 760 765	2306
aac ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu 770 775 780	2354
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Ser	Leu	Ile	Pro	Leu	Glu	Arg	Ala	Val	Ile	Asn	Gly	Gln	Leu	Tyr	Glu		
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Glu	Ser	Glu	Asn	Gln	Asp	Glu	Asp	Pro	Asn	Asp	Glu	Gly	Ser	Val	Leu		
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Ser	Phe	Lys	Cys	Ser	Gln	Ser	Thr	Pro	Cys	Pro	Val	Asn	Arg	Lys	Leu		
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tgg	att	ccc	tgg	atg	aaa	tcc	aag	gag	ggc	cat	ctt	cag	aat	gga	aaa	2642	
Trp	Ile	Pro	Trp	Met	Lys	Ser	Lys	Glu	Gly	His	Leu	Gln	Asn	Gly	Lys		
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atg	caa	act	aaa	ccc	aat	gcc	aac	ttt	gtg	caa	cct	gga	gat	cta	gtc	2690	
Met	Gln	Thr	Lys	Pro	Asn	Ala	Asn	Phe	Val	Gln	Pro	Gly	Asp	Leu	Val		
			880				885								890		
cta	agc	cac	aca	cct	ggg	cag	cca	ctt	cat	ata	aag	gtt	act	cca	gac	2738	
Leu	Ser	His	Thr	Pro	Gly	Gln	Pro	Leu	His	Ile	Lys	Val	Thr	Pro	Asp		
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cat	gta	caa	aac	aca	gcc	act	ctt	gaa	atc	aca	agt	cca	acc	aca	gag	2786	
His	Val	Gln	Asn	Thr	Ala	Thr	Leu	Glu	Ile	Thr	Ser	Pro	Thr	Thr	Glu		
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agt	cct	cac	tct	tac	acg	agt	act	gca	gtg	ata	ccg	aac	tgt	ggc	acg	2834	
Ser	Pro	His	Ser	Tyr	Thr	Ser	Thr	Ala	Val	Ile	Pro	Asn	Cys	Gly	Thr		
				930						935					940		
cca	aag	caa	agg	ata	acc	atc	ctc	caa	aac	gcc	tcc	ata	aca	cca	gta	2882	
Pro	Lys	Gln	Arg	Ile	Thr	Ile	Leu	Gln	Asn	Ala	Ser	Ile	Thr	Pro	Val		
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aag	tcc	aaa	acc	tct	acc	gaa	gac	ctc	atg	aat	tta	gaa	caa	ggc	atg	2930	
Lys	Ser	Lys	Thr	Ser	Thr	Glu	Asp	Leu	Met	Asn	Leu	Glu	Gln	Gly	Met		
				960			965								970		
tcc	cca	att	acc	atg	gca	acc	ttt	gcc	aga	gca	cag	acc	cca	gag	tct	2978	
Ser	Pro	Ile	Thr	Met	Ala	Thr	Phe	Ala	Arg	Ala	Gln	Thr	Pro	Glu	Ser		
				975			980								985		
tgt	ggt	tct	cta	act	cca	gaa	agg	aca	atg	tcc	cct	att	cag	gtt	ttg	3026	
Cys	Gly	Ser	Leu	Thr	Pro	Glu	Arg	Thr	Met	Ser	Pro	Ile	Gln	Val	Leu		
990						995				1000					1005		
gct	gtg	act	ggt	tca	gct	agc	tct	cct	gag	cag	gga	cgc	tcc	cca		3071	
Ala	Val	Thr	Gly	Ser	Ala	Ser	Ser	Pro	Glu	Gln	Gly	Arg	Ser	Pro			
				1010					1015					1020			
gaa	cca	aca	gaa	atc	agt	gcc	aag	cat	gcg	ata	ttc	aga	gtc	tcc		3116	
Glu	Pro	Thr	Glu	Ile	Ser	Ala	Lys	His	Ala	Ile	Phe	Arg	Val	Ser			
				1025					1030					1035			
cca	gac	cgg	cag	tca	tca	tgg	cag	ttt	cag	cgt	tca	aac	agc	aat		3161	
Pro	Asp	Arg	Gln	Ser	Ser	Trp	Gln	Phe	Gln	Arg	Ser	Asn	Ser	Asn			

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Ser Ser Ser Val Ile	Thr Thr Glu Asp Asn	Lys Ile His Ile His	
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tta gga agt cct tac	atg caa gct gta gcc	agc cct gtg aga cct	3251
Leu Gly Ser Pro Tyr	Met Gln Ala Val Ala	Ser Pro Val Arg Pro	
1070	1075	1080	
gcc agc cct tca gca	cca ctg cag gat aac	cga act caa ggc tta	3296
Ala Ser Pro Ser Ala	Pro Leu Gln Asp Asn	Arg Thr Gln Gly Leu	
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att aac ggg gca cta	aac aaa aca acc aat	aaa gtc acc agc agt	3341
Ile Asn Gly Ala Leu	Asn Lys Thr Thr Asn	Lys Val Thr Ser Ser	
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Ile Thr Ile Thr Pro	Thr Ala Thr Pro Leu	Pro Arg Gln Ser Gln	
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Ile Thr Val Ser Asn	Ile Tyr Asn		
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 35 40 45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala  
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Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu  
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Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu  
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Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro  
 100 105 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser  
 115 120 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp  
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Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln  
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Leu Leu Val Ala Glu Lys Ser His Arg Gln Thr Ile Leu Glu Leu Glu  
 165 170 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe  
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Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp  
 195 200 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg  
 210 215 220

Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu  
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Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln  
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Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr  
 260 265 270

Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala  
 275 280 285

Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln  
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Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn  
 305 310 315 320



Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu  
325 330 335

Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln  
340 345 350

Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile  
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Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met Glu Gly  
370 375 380

Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp Leu Asn  
385 390 395 400

Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys Leu Glu  
405 410 415

Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu Glu Asp  
420 425 430

Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys Asn Leu  
435 440 445

Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu Glu Ser  
450 455 460

Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg Leu Glu  
465 470 475 480

Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys Thr Leu  
485 490 495

Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys Leu Lys  
500 505 510

Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln Val Glu  
515 520 525

Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu Thr Lys  
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Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr Ser Val

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 Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu Glu Glu  
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 Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn Arg Leu  
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 Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys Leu Asn  
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 Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn Asn Lys  
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 Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys Leu Lys  
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 Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp Glu Tyr  
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 Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala Gln Phe  
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 Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys Tyr Lys  
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 Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe Lys Arg  
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 Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu Asn Gln  
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 Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn Leu Thr  
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 Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg Pro Ser  
                                  770                                   775                                   780

Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys Glu Val  
785 790 795 800

Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser Leu Ile  
805 810 815

Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu Ser Glu  
820 825 830

Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser Phe Lys  
835 840 845

Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp Ile Pro  
850 855 860

Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met Gln Thr  
865 870 875 880

Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu Ser His  
885 890 895

Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His Val Gln  
900 905 910

Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser Pro His  
915 920 925

Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro Lys Gln  
930 935 940

Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys Ser Lys  
945 950 955 960

Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser Pro Ile  
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Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys Gly Ser  
980 985 990

Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala Val Thr  
995 1000 1005

Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro Thr  
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Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg  
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Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser  
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Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser  
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Pro Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro  
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Ser Ala Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly  
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ata ctt ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc cac Ile Leu Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His 50 55 60	194
caa gca gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc att Gln Ala Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile 65 70 75	242
ctg gag gga gaa ctg cag gct cga gat gag gtc ata ggc att tta aag Leu Glu Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys 80 85 90	290
gct gaa aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt gtc Ala Glu Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val 95 100 105 110	338
act cca aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa gcg Thr Pro Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala 115 120 125	386
aaa tct acc cct tgg cag gag gac atc tat gag aaa cca atg aat gag Lys Ser Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu 130 135 140	434
ttg gac aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg Leu Asp Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu 145 150 155	482
gga cag ctt tta gtg gca gaa aaa tcc cgt agg caa acc ata ttg gag Gly Gln Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu 160 165 170	530
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Leu Gln Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr	
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cat acc aaa cta gcc ctt gct gaa gcc aga gtt cag gag gaa gag cag	866
His Thr Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln	
275 280 285	
aag gca acc aga cta gag aag gaa ctg caa acg cag acc aca aag ttt	914
Lys Ala Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe	
290 295 300	
cac caa gac caa gac aca att atg gcg aag ctc acc aat gag gac agt	962
His Gln Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser	
305 310 315	
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Gln Asn Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile	
320 325 330	
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Asp Glu Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu	
335 340 345 350	
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Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp	
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Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys	
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Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu	
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Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys	
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Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu	
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Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg	

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Leu Glu Lys Thr Glu Phe Thr	Leu Lys Glu Asp Leu Thr Lys Leu Lys		
480	485	490	
aca tta act gtg atg ttt gta gat gaa cgg aaa	aca atg agt gaa aaa		1538
Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys	Thr Met Ser Glu Lys		
495	500	505	510
tta aag aaa act gaa gat aaa tta caa gct gct tct tct cag ctt caa			1586
Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln			
515	520	525	
gtg gag caa aat aaa gta aca aca gtt act gag aag tta att gag gaa			1634
Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu			
530	535	540	
act aaa agg gcg ctc aag tcc aaa acc gat gta gaa gaa aag atg tac			1682
Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr			
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Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu			
560	565	570	
gaa gag aaa gga aat gat ctc ctg tca aga gtt aat atg ttg aaa aat			1778
Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn			
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Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys			
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tta aat caa gac tct ggg aaa tcc aca aca gca tta cac caa gaa aac			1874
Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn			
610	615	620	
aat aag att aag gag ctc tct caa gaa gtg gaa aga ctg aaa ctg aag			1922
Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys			
625	630	635	
cta aag gac atg aaa gcc att gag gat gac ctc atg aaa aca gaa gat			1970
Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp			
640	645	650	
gaa tat gag act cta gaa cga agg tat gct aat gaa cga gac aaa gct			2018
Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala			
655	660	665	670
caa ttt tta tct aaa gag cta gaa cat gtt aaa atg gaa ctt gct aag			2066
Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys			
675	680	685	
tac aag tta gca gaa aag aca gag acc agc cat gaa caa tgg ctt ttc			2114
Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe			
690	695	700	

aaa agg ctt caa gaa gaa gaa gct aag tca ggg cac ctc tca aga gaa Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu 705 710 715	2162
gtg gat gca tta aaa gag aaa att cat gaa tac atg gca act gaa gac Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp 720 725 730	2210
cta ata tgt cac ctc cag gga gat cac tca gtc ctg caa aaa aaa cta Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu 735 740 745 750	2258
aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa aac Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn 755 760 765	2306
ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc agg Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg 770 775 780	2354
cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct aaa Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys 785 790 795	2402
gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag agc Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser 800 805 810	2450
ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag gag Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu 815 820 825 830	2498
agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg tcc Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser 835 840 845	2546
ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta tgg Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp 850 855 860	2594
att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa atg Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met 865 870 875	2642
caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc cta Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu 880 885 890	2690
agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac cat Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His 895 900 905 910	2738
gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag agt Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser 915 920 925	2786



cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg cca Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro 930 935 940	2834
aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta aag Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys 945 950 955	2882
tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg tcc Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser 960 965 970	2930
cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct tgt Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys 975 980 985 990	2978
ggc tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg gct Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala 995 1000 1005	3026
gtg act ggt tca gct agc tct cct gag cag gga cgc tcc cca gaa Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu 1010 1015 1020	3071
cca aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro 1025 1030 1035	3116
gac cgg cag tca tca tgg cag ttt cag cgt tca aac agc aat agc Asp Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser 1040 1045 1050	3161
tca agt gtg ata act act gag gat aat aaa atc cac att cac tta Ser Ser Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu 1055 1060 1065	3206
gga agt cct tac atg caa gct gta gcc agc cct gtg aga cct gcc Gly Ser Pro Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala 1070 1075 1080	3251
agc cct tca gca cca ctg cag gat aac cga act caa ggc tta att Ser Pro Ser Ala Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile 1085 1090 1095	3296
aac ggg gca cta aac aaa aca acc aat aaa gtc acc agc agt att Asn Gly Ala Leu Asn Lys Thr Thr Asn Lys Val Thr Ser Ser Ile 1100 1105 1110	3341
act atc aca cca aca gcc aca cct ctt cct cga caa tca caa att Thr Ile Thr Pro Thr Ala Thr Pro Leu Pro Arg Gln Ser Gln Ile 1115 1120 1125	3386
aca gta agt aat ata tat aac tgaccacgc Thr Val Ser Asn Ile Tyr Asn 1130	3416

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 <212> PRT  
 <213> Homo sapiens

<400> 16

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 20 25 30

His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu  
 35 40 45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala  
 50 55 60

Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu  
 65 70 75 80

Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu  
 85 90 95

Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro  
 100 105 110

Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser  
 115 120 125

Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp  
 130 135 140

Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln  
 145 150 155 160

Leu Leu Val Ala Glu Lys Ser Arg Arg Gln Thr Ile Leu Glu Leu Glu  
 165 170 175

Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe  
 180 185 190

Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp  
 195 200 205

Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg  
 210 215 220

Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu  
 225 230 235 240

Met Val Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln  
 245 250 255

Arg Gln Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr  
 260 265 270

Lys Leu Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala  
 275 280 285

Thr Arg Leu Glu Lys Glu Leu Gln Thr Gln Thr Thr Lys Phe His Gln  
 290 295 300

Asp Gln Asp Thr Ile Met Ala Lys Leu Thr Asn Glu Asp Ser Gln Asn  
 305 310 315 320

Arg Gln Leu Gln Gln Lys Leu Ala Ala Leu Ser Arg Gln Ile Asp Glu  
 325 330 335

Leu Glu Glu Thr Asn Arg Ser Leu Arg Lys Ala Glu Glu Glu Leu Gln  
 340 345 350

Asp Ile Lys Glu Lys Ile Ser Lys Gly Glu Tyr Gly Asn Ala Gly Ile  
 355 360 365

Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met Glu Gly  
 370 375 380

Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp Leu Asn  
 385 390 395 400

Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys Leu Glu  
 405 410 415

Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu Glu Asp  
 420 425 430

Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys Asn Leu  
 435 440 445

Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu Glu Ser  
 450 455 460

Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg Leu Glu  
 465 470 475 480

Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys Thr Leu  
 485 490 495

Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys Leu Lys  
 500 505 510

Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln Val Glu  
 515 520 525

Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu Thr Lys  
 530 535 540

Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr Ser Val  
 545 550 555 560

Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu Glu Glu  
 565 570 575

Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn Arg Leu  
 580 585 590

Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys Leu Asn  
 595 600 605

Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn Asn Lys  
 610 615 620

Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys Leu Lys  
 625 630 635 640

Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp Glu Tyr  
 645 650 655

Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala Gln Phe  
660 665 670

Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys Tyr Lys  
675 680 685

Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe Lys Arg  
690 695 700

Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu Val Asp  
705 710 715 720

Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp Leu Ile  
725 730 735

Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu Asn Gln  
740 745 750

Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn Leu Thr  
755 760 765

Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg Pro Ser  
770 775 780

Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys Glu Val  
785 790 795 800

Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser Leu Ile  
805 810 815

Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu Ser Glu  
820 825 830

Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser Phe Lys  
835 840 845

Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp Ile Pro  
850 855 860

Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met Gln Thr  
865 870 875 880

Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu Ser His

885	890	895
Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His Val Gln		
900	905	910
Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser Pro His		
915	920	925
Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro Lys Gln		
930	935	940
Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys Ser Lys		
945	950	955
Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser Pro Ile		
965	970	975
Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys Gly Ser		
980	985	990
Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala Val Thr		
995	1000	1005
Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro Thr		
1010	1015	1020
Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg		
1025	1030	1035
Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser		
1040	1045	1050
Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser		
1055	1060	1065
Pro Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro		
1070	1075	1080
Ser Ala Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly		
1085	1090	1095
Ala Leu Asn Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile		
1100	1105	1110

Thr Pro Thr Ala Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val  
 1115 1120 1125

Ser Asn Ile Tyr Asn  
 1130

<210> 17  
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 <212> DNA  
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<220>  
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 <222> (1)..(45)  
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<400> 17  
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 Thr Lys Ser Thr Arg Lys Gln Glu Gln Arg Phe Arg Lys Arg Asp  
 1 5 10 15

<210> 18  
 <211> 15  
 <212> PRT  
 <213> Homo sapiens

<400> 18

Thr Lys Ser Thr Arg Lys Gln Glu Gln Arg Phe Arg Lys Arg Asp  
 1 5 10 15

<210> 19  
 <211> 90  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(90)  
 <223>

<400> 19  
 gtg gat gaa cag caa agg ctg acg gca cag ctc acc ctt caa aga cag 48  
 Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln  
 1 5 10 15

aaa atc caa gag ctg acc aca aat gca aag gaa aca cat acc 90  
 Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr  
 20 25 30

<210> 20  
 <211> 30  
 <212> PRT  
 <213> Homo sapiens

- <400> 20

Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln  
 1 5 10 15

Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr  
 20 25 30

<210> 21  
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 <212> DNA  
 <213> Homo sapiens

<220>  
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 <222> (1)..(1158)  
 <223>

<400> 21  
 cta aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa 48  
 Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu  
 1 5 10 15  
 aac ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc 96  
 Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu  
 20 25 30  
 agg cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct 144  
 Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser  
 35 40 45  
 aaa gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag 192  
 Lys Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys  
 50 55 60  
 agc ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag 240  
 Ser Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu  
 65 70 75 80  
 gag agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg 288  
 Glu Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu  
 85 90 95  
 tcc ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta 336  
 Ser Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu  
 100 105 110  
 tgg att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa 384  
 Trp Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys  
 115 120 125



atg caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc Met Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val 130 135 140	432
cta agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac Leu Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp 145 150 155 160	480
cat gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag His Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu 165 170 175	528
agt cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg Ser Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr 180 185 190	576
cca aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta Pro Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val 195 200 205	624
aag tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg Lys Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met 210 215 220	672
tcc cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct Ser Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser 225 230 235 240	720
tgt ggt tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg Cys Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu 245 250 255	768
gct gtg act ggt tca gct agc tct cct gag cag gga cgc tcc cca gaa Ala Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu 260 265 270	816
cca aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca gac Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp 275 280 285	864
cgg cag tca tca tgg cag ttt cag cgt tca aac agc aat agc tca agt Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser 290 295 300	912
gtg ata act act gag gat aat aaa atc cac att cac tta gga agt cct Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro 305 310 315 320	960
tac atg caa gct gta gcc agc cct gtg aga cct gcc agc cct tca gca Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala 325 330 335	1008
cca ctg cag gat aac cga act caa ggc tta att aac ggg gca cta aac Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn 340 345 350	1056

aaa aca acc aat aaa gtc acc agc agt att act atc aca cca aca gcc 1104  
 Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala  
 355 360 365

aca cct ctt cct cga caa tca caa att aca gtg gaa cca ctt ctt ctg 1152  
 Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Glu Pro Leu Leu Leu  
 370 375 380

cct cat 1158  
 Pro His  
 385

<210> 22  
 <211> 386  
 <212> PRT  
 <213> Homo sapiens.

<400> 22

Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu  
 1 5 10 15

Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu  
 20 25 30

Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser  
 35 40 45

Lys Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys  
 50 55 60

Ser Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu  
 65 70 75 80

Glu Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu  
 85 90 95

Ser Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu  
 100 105 110

Trp Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys  
 115 120 125

Met Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val  
 130 135 140

Leu Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp

145                      150                      155                      160  
 His Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu  
                                  165                      170                      175  
 Ser Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr  
                                  180                      185                      190  
 Pro Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val  
                                  195                      200                      205  
 Lys Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met  
                                  210                      215                      220  
 Ser Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser  
                                  225                      230                      235                      240  
 Cys Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu  
                                  245                      250                      255  
 Ala Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu  
                                  260                      265                      270  
 Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp  
                                  275                      280                      285  
 Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser  
                                  290                      295                      300  
 Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro  
                                  305                      310                      315                      320  
 Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala  
                                  325                      330                      335  
 Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn  
                                  340                      345                      350  
 Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala  
                                  355                      360                      365  
 Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Glu Pro Leu Leu Leu  
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Pro His  
385

<210> 23  
<211> 2355  
<212> DNA  
<213> Homo sapiens

<220>  
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1 5 10 15  
ggt atc atg gct gaa gtg gaa gag ctc agg aaa cgt gtg cta gat atg 96  
Gly Ile Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met  
20 25 30  
gaa ggg aaa gat gaa gag ctc ata aaa atg gag gag cag tgc aga gat 144  
Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp  
35 40 45  
ctc aat aag agg ctt gaa agg gag acg tta cag agt aaa gac ttt aaa 192  
Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys  
50 55 60  
cta gag gtt gaa aaa ctc agt aaa aga att atg gct ctg gaa aag tta 240  
Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu  
65 70 75 80  
gaa gac gct ttc aac aaa agc aaa caa gaa tgc tac tct ctg aaa tgc 288  
Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys  
85 90 95  
aat tta gaa aaa gaa agg atg acc aca aag cag ttg tct caa gaa ctg 336  
Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu  
100 105 110  
gag agt tta aaa gta agg atc aaa gag cta gaa gcc att gaa agt cgg 384  
Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg  
115 120 125  
cta gaa aag aca gaa ttc act cta aaa gag gat tta act aaa ctg aaa 432  
Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys  
130 135 140  
aca tta act gtg atg ttt gta gat gaa cgg aaa aca atg agt gaa aaa 480  
Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys  
145 150 155 160

tta aag aaa act gaa gat aaa tta caa gct gct tct tct cag ctt caa Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln 165 170 175	528
gtg gag caa aat aaa gta aca aca gtt act gag aag tta att gag gaa Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu 180 185 190	576
act aaa agg gcg ctc aag tcc aaa acc gat gta gaa gaa aag atg tac Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr 195 200 205	624
agc gta acc aag gag aga gat gat tta aaa aac aaa ttg aaa gcg gaa Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu 210 215 220	672
gaa gag aaa gga aat gat ctc ctg tca aga gtt aat atg ttg aaa aat Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn 225 230 235 240	720
agg ctt caa tca ttg gaa gca att gag aaa gat ttc cta aaa aac aaa Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys 245 250 255	768
tta aat caa gac tct ggg aaa tcc aca aca gca tta cac caa gaa aac Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn 260 265 270	816
aat aag att aag gag ctc tct caa gaa gtg gaa aga ctg aaa ctg aag Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys 275 280 285	864
cta aag gac atg aaa gcc att gag gat gac ctc atg aaa aca gaa gat Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp 290 295 300	912
gaa tat gag act cta gaa cga agg tat gct aat gaa cga gac aaa gct Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala 305 310 315 320	960
caa ttt tta tct aaa gag cta gaa cat gtt aaa atg gaa ctt gct aag Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys 325 330 335	1008
tac aag tta gca gaa aag aca gag acc agc cat gaa caa tgg ctt ttc Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe 340 345 350	1056
aaa agg ctt caa gaa gaa gaa gct aag tca ggg cac ctc tca aga gaa Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu 355 360 365	1104
gtg gat gca tta aaa gag aaa att cat gaa tac atg gca act gaa gac Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp 370 375 380	1152
cta ata tgt cac ctc cag gga gat cac tca gtc ctg caa aaa aaa cta	1200

Leu 385	Ile	Cys	His	Leu	Gln	Gly	Asp	His	Ser	Val	Leu	Gln	Lys	Lys	Leu	
					390					395					400	
aat	caa	caa	gaa	aac	agg	aac	aga	gat	tta	gga	aga	gag	att	gaa	aac	1248
Asn	Gln	Gln	Glu	Asn	Arg	Asn	Arg	Asp	Leu	Gly	Arg	Glu	Ile	Glu	Asn	
				405					410					415		
ctc	act	aag	gag	tta	gag	agg	tac	cgg	cat	ttc	agt	aag	agc	ctc	agg	1296
Leu	Thr	Lys	Glu	Leu	Glu	Arg	Tyr	Arg	His	Phe	Ser	Lys	Ser	Leu	Arg	
			420					425					430			
cct	agt	ctc	aat	gga	aga	aga	att	tcc	gat	cct	caa	gta	ttt	tct	aaa	1344
Pro	Ser	Leu	Asn	Gly	Arg	Arg	Ile	Ser	Asp	Pro	Gln	Val	Phe	Ser	Lys	
		435					440					445				
gaa	gtt	cag	aca	gaa	gca	gta	gac	aat	gaa	cca	cct	gat	tac	aag	agc	1392
Glu	Val	Gln	Thr	Glu	Ala	Val	Asp	Asn	Glu	Pro	Pro	Asp	Tyr	Lys	Ser	
	450					455					460					
ctc	att	cct	ctg	gaa	cgt	gca	gtc	atc	aat	ggc	cag	tta	tat	gag	gag	1440
Leu	Ile	Pro	Leu	Glu	Arg	Ala	Val	Ile	Asn	Gly	Gln	Leu	Tyr	Glu	Glu	
465					470					475					480	
agt	gag	aat	caa	gac	gag	gac	cct	aat	gat	gag	gga	tct	gtg	ctg	tcc	1488
Ser	Glu	Asn	Gln	Asp	Glu	Asp	Pro	Asn	Asp	Glu	Gly	Ser	Val	Leu	Ser	
				485					490					495		
ttc	aaa	tgc	agc	cag	tct	act	cca	tgt	cct	gtt	aac	aga	aag	cta	tgg	1536
Phe	Lys	Cys	Ser	Gln	Ser	Thr	Pro	Cys	Pro	Val	Asn	Arg	Lys	Leu	Trp	
			500					505					510			
att	ccc	tgg	atg	aaa	tcc	aag	gag	ggc	cat	ctt	cag	aat	gga	aaa	atg	1584
Ile	Pro	Trp	Met	Lys	Ser	Lys	Glu	Gly	His	Leu	Gln	Asn	Gly	Lys	Met	
		515					520					525				
caa	act	aaa	ccc	aat	gcc	aac	ttt	gtg	caa	cct	gga	gat	cta	gtc	cta	1632
Gln	Thr	Lys	Pro	Asn	Ala	Asn	Phe	Val	Gln	Pro	Gly	Asp	Leu	Val	Leu	
	530					535					540					
agc	cac	aca	cct	ggg	cag	cca	ctt	cat	ata	aag	gtt	act	cca	gac	cat	1680
Ser	His	Thr	Pro	Gly	Gln	Pro	Leu	His	Ile	Lys	Val	Thr	Pro	Asp	His	
545					550					555					560	
gta	caa	aac	aca	gcc	act	ctt	gaa	atc	aca	agt	cca	acc	aca	gag	agt	1728
Val	Gln	Asn	Thr	Ala	Thr	Leu	Glu	Ile	Thr	Ser	Pro	Thr	Thr	Glu	Ser	
				565					570					575		
cct	cac	tct	tac	acg	agt	act	gca	gtg	ata	ccg	aac	tgt	ggc	acg	cca	1776
Pro	His	Ser	Tyr	Thr	Ser	Thr	Ala	Val	Ile	Pro	Asn	Cys	Gly	Thr	Pro	
			580					585					590			
aag	caa	agg	ata	acc	atc	ctc	caa	aac	gcc	tcc	ata	aca	cca	gta	aag	1824
Lys	Gln</															

610	615	620	
cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct tgt			1920
Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys			
625	630	635	640
ggt tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg gct			1968
Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala			
645	650	655	
gtg act ggt tca gct agc tct cct gag cag gga cgc tcc cca gaa cca			2016
Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro			
660	665	670	
aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca gac cgg			2064
Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg			
675	680	685	
cag tca tca tgg cag ttt cag cgt tca aac agc aat agc tca agt gtg			2112
Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser Val			
690	695	700	
ata act act gag gat aat aaa atc cac att cac tta gga agt cct tac			2160
Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro Tyr			
705	710	715	720
atg caa gct gta gcc agc cct gtg aga cct gcc agc cct tca gca cca			2208
Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala Pro			
725	730	735	
ctg cag gat aac cga act caa ggc tta att aac ggg gca cta aac aaa			2256
Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn Lys			
740	745	750	
aca acc aat aaa gtc acc agc agt att act atc aca cca aca gcc aca			2304
Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala Thr			
755	760	765	
cct ctt cct cga caa tca caa att aca gtg gaa cca ctt ctt ctg cct			2352
Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Glu Pro Leu Leu Leu Pro			
770	775	780	
cat			2355
His			
785			

&lt;210&gt; 24

&lt;211&gt; 785

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 24

Leu	Gln	Asp	Ile	Lys	Glu	Lys	Ile	Ser	Lys	Gly	Glu	Tyr	Gly	Asn	Ala
1				5					10					15	

Gly Ile Met Ala Glu Val Glu Glu Leu Arg Lys Arg Val Leu Asp Met  
20 25 30

Glu Gly Lys Asp Glu Glu Leu Ile Lys Met Glu Glu Gln Cys Arg Asp  
35 40 45

Leu Asn Lys Arg Leu Glu Arg Glu Thr Leu Gln Ser Lys Asp Phe Lys  
50 55 60

Leu Glu Val Glu Lys Leu Ser Lys Arg Ile Met Ala Leu Glu Lys Leu  
65 70 75 80

Glu Asp Ala Phe Asn Lys Ser Lys Gln Glu Cys Tyr Ser Leu Lys Cys  
85 90 95

Asn Leu Glu Lys Glu Arg Met Thr Thr Lys Gln Leu Ser Gln Glu Leu  
100 105 110

Glu Ser Leu Lys Val Arg Ile Lys Glu Leu Glu Ala Ile Glu Ser Arg  
115 120 125

Leu Glu Lys Thr Glu Phe Thr Leu Lys Glu Asp Leu Thr Lys Leu Lys  
130 135 140

Thr Leu Thr Val Met Phe Val Asp Glu Arg Lys Thr Met Ser Glu Lys  
145 150 155 160

Leu Lys Lys Thr Glu Asp Lys Leu Gln Ala Ala Ser Ser Gln Leu Gln  
165 170 175

Val Glu Gln Asn Lys Val Thr Thr Val Thr Glu Lys Leu Ile Glu Glu  
180 185 190

Thr Lys Arg Ala Leu Lys Ser Lys Thr Asp Val Glu Glu Lys Met Tyr  
195 200 205

Ser Val Thr Lys Glu Arg Asp Asp Leu Lys Asn Lys Leu Lys Ala Glu  
210 215 220

Glu Glu Lys Gly Asn Asp Leu Leu Ser Arg Val Asn Met Leu Lys Asn  
225 230 235 240



Arg Leu Gln Ser Leu Glu Ala Ile Glu Lys Asp Phe Leu Lys Asn Lys  
245 250 255

Leu Asn Gln Asp Ser Gly Lys Ser Thr Thr Ala Leu His Gln Glu Asn  
260 265 270

Asn Lys Ile Lys Glu Leu Ser Gln Glu Val Glu Arg Leu Lys Leu Lys  
275 280 285

Leu Lys Asp Met Lys Ala Ile Glu Asp Asp Leu Met Lys Thr Glu Asp  
290 295 300

Glu Tyr Glu Thr Leu Glu Arg Arg Tyr Ala Asn Glu Arg Asp Lys Ala  
305 310 315 320

Gln Phe Leu Ser Lys Glu Leu Glu His Val Lys Met Glu Leu Ala Lys  
325 330 335

Tyr Lys Leu Ala Glu Lys Thr Glu Thr Ser His Glu Gln Trp Leu Phe  
340 345 350

Lys Arg Leu Gln Glu Glu Glu Ala Lys Ser Gly His Leu Ser Arg Glu  
355 360 365

Val Asp Ala Leu Lys Glu Lys Ile His Glu Tyr Met Ala Thr Glu Asp  
370 375 380

Leu Ile Cys His Leu Gln Gly Asp His Ser Val Leu Gln Lys Lys Leu  
385 390 395 400

Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu Asn  
405 410 415

Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu Arg  
420 425 430

Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser Lys  
435 440 445

Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys Ser  
450 455 460

Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu Glu

465		470		475		480
Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu Ser	485		490		495	
Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu Trp	500		505		510	
Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys Met	515		520		525	
Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val Leu	530		535		540	
Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp His	545		550		555	560
Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu Ser	565		570		575	
Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr Pro	580		585		590	
Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val Lys	595		600		605	
Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met Ser	610		615		620	
Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser Cys	625		630		635	640
Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu Ala	645		650		655	
Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu Pro	660		665		670	
Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp Arg	675		680		685	
Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser Val	690		695		700	

Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro Tyr  
 705 710 715 720

Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala Pro  
 725 730 735

Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn Lys  
 740 745 750

Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala Thr  
 755 760 765

Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Glu Pro Leu Leu Leu Pro  
 770 775 780

His  
 785

<210> 25  
 <211> 21  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(21)  
 <223>

<400> 25  
 gaa cca ctt ctt ctg cct cat  
 Glu Pro Leu Leu Leu Pro His  
 1 5

21

<210> 26  
 <211> 7  
 <212> PRT  
 <213> Homo sapiens

<400> 26

Glu Pro Leu Leu Leu Pro His  
 1 5

<210> 27  
 <211> 30  
 <212> DNA  
 <213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(30)  
<223>

<400> 27  
ttg gac aaa gtt gtg gaa aaa cat aaa gaa  
Leu Asp Lys Val Val Glu Lys His Lys Glu  
1 5 10

30

<210> 28  
<211> 10  
<212> PRT  
<213> Homo sapiens

<400> 28  
Leu Asp Lys Val Val Glu Lys His Lys Glu  
1 5 10

<210> 29  
<211> 30  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS  
<222> (1)..(30)  
<223>

<400> 29  
gag gaa gag cag aag gca acc aga cta gag  
Glu Glu Glu Gln Lys Ala Thr Arg Leu Glu  
1 5 10

30

<210> 30  
<211> 10  
<212> PRT  
<213> Homo sapiens

<400> 30  
Glu Glu Glu Gln Lys Ala Thr Arg Leu Glu  
1 5 10

<210> 31  
<211> 60  
<212> DNA  
<213> Homo sapiens

<220>  
<221> CDS

&lt;222&gt; (1)..(60)

&lt;223&gt;

&lt;400&gt; 31

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ttg gac aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg      48
- Leu Asp Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu
  1              5              10              15

```

```

gga cag ctt tta      60
Gly Gln Leu Leu
      20

```

&lt;210&gt; 32

&lt;211&gt; 20

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens.

&lt;400&gt; 32

```

Leu Asp Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu
  1              5              10              15

```

```

Gly Gln Leu Leu
      20

```

&lt;210&gt; 33

&lt;211&gt; 150

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(150)

&lt;223&gt;

&lt;400&gt; 33

```

gtg gat gaa cag caa agg ctg acg gca cag ctc acc ctt caa aga cag      48
Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln
  1              5              10              15

```

```

aaa atc caa gag ctg acc aca aat gca aag gaa aca cat acc aaa cta      96
Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr Lys Leu
      20              25              30

```

```

gcc ctt gct gaa gcc aga gtt cag gag gaa gag cag aag gca acc aga      144
Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala Thr Arg
      35              40              45

```

```

cta gag      150
Leu Glu
      50

```

&lt;210&gt; 34

<211> 50  
 <212> PRT  
 <213> Homo sapiens

<400> 34

Val Asp Glu Gln Gln Arg Leu Thr Ala Gln Leu Thr Leu Gln Arg Gln  
 1 5 10 15

Lys Ile Gln Glu Leu Thr Thr Asn Ala Lys Glu Thr His Thr Lys Leu  
 20 25 30

Ala Leu Ala Glu Ala Arg Val Gln Glu Glu Glu Gln Lys Ala Thr Arg  
 35 40 45

Leu Glu  
 50

<210> 35  
 <211> 720  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(720)  
 <223>

<400> 35

atg cgt tcc aga ggc agt gat acc gag ggc tca gcc caa aag aaa ttt 48  
 Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys Lys Phe  
 1 5 10 15

cca aga cat act aaa ggc cac agt ttc caa ggg cct aaa aac atg aag 96  
 Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys  
 20 25 30

cat aga cag caa gac aaa gac tcc ccc agt gag tcg gat gta ata ctt 144  
 His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu  
 35 40 45

ccg tgt ccc aag gca gag aag cca cac agt ggt aat ggc cac caa gca 192  
 Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala  
 50 55 60

gaa gac ctc tca aga gat gac ctg tta ttt ctc ctc agc att ctg gag 240  
 Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu  
 65 70 75 80

gga gaa ctg cag gct cga gat gag gtc ata ggc att tta aag gct gaa 288  
 Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Glu Ile Leu Lys Ala Glu  
 85 90 95

aaa atg gac ctg gct ttg ctg gaa gct cag tat ggg ttt gtc act cca 336  
 Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro  
 100 105 110

aaa aag gtg tta gag gct ctc cag aga gat gct ttt caa gcg aaa tct 384  
 Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser  
 115 120 125

acc cct tgg cag gag gac atc tat gag aaa cca atg aat gag ttg gac 432  
 Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp  
 130 135 140

aaa gtt gtg gaa aaa cat aaa gaa tct tac aga cga atc ctg gga cag 480  
 Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln  
 145 150 155 160

ctt tta gtg gca gaa aaa tcc cat agg caa acc ata ttg gag ttg gag 528  
 Leu Leu Val Ala Glu Lys Ser His Arg Gln Thr Ile Leu Glu Leu Glu  
 165 170 175

gaa gaa aag aga aaa cat aaa gaa tac atg gag aag agt gat gaa ttc 576  
 Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe  
 180 185 190

ata tgc cta cta gaa cag gaa tgt gaa aga tta aag aag cta att gat 624  
 Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp  
 195 200 205

caa gaa atc aag tct cag gag gag aag gag caa gaa aag gag aaa agg 672  
 Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg  
 210 215 220

gtc acc acc ctg aaa gag gag ctg acc aag ctg aag tct ttt gct ttg 720  
 Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu  
 225 230 235 240

<210> 36  
 <211> 240  
 <212> PRT  
 <213> Homo sapiens

<400> 36

Met Arg Ser Arg Gly Ser Asp Thr Glu Gly Ser Ala Gln Lys Lys Phe  
 1 5 10 15

Pro Arg His Thr Lys Gly His Ser Phe Gln Gly Pro Lys Asn Met Lys  
 20 25 30

His Arg Gln Gln Asp Lys Asp Ser Pro Ser Glu Ser Asp Val Ile Leu  
 35 40 45

Pro Cys Pro Lys Ala Glu Lys Pro His Ser Gly Asn Gly His Gln Ala

50                                      55                                      60  
 Glu Asp Leu Ser Arg Asp Asp Leu Leu Phe Leu Leu Ser Ile Leu Glu  
 65                                      70                                      75                                      80  
 Gly Glu Leu Gln Ala Arg Asp Glu Val Ile Gly Ile Leu Lys Ala Glu  
                                     85                                      90                                      95  
 Lys Met Asp Leu Ala Leu Leu Glu Ala Gln Tyr Gly Phe Val Thr Pro  
                                     100                                      105                                      110  
 Lys Lys Val Leu Glu Ala Leu Gln Arg Asp Ala Phe Gln Ala Lys Ser  
                                     115                                      120                                      125  
 Thr Pro Trp Gln Glu Asp Ile Tyr Glu Lys Pro Met Asn Glu Leu Asp  
                                     130                                      135                                      140  
 Lys Val Val Glu Lys His Lys Glu Ser Tyr Arg Arg Ile Leu Gly Gln  
 145                                      150                                      155                                      160  
 Leu Leu Val Ala Glu Lys Ser His Arg Gln Thr Ile Leu Glu Leu Glu  
                                     165                                      170                                      175  
 Glu Glu Lys Arg Lys His Lys Glu Tyr Met Glu Lys Ser Asp Glu Phe  
                                     180                                      185                                      190  
 Ile Cys Leu Leu Glu Gln Glu Cys Glu Arg Leu Lys Lys Leu Ile Asp  
                                     195                                      200                                      205  
 Gln Glu Ile Lys Ser Gln Glu Glu Lys Glu Gln Glu Lys Glu Lys Arg  
                                     210                                      215                                      220  
 Val Thr Thr Leu Lys Glu Glu Leu Thr Lys Leu Lys Ser Phe Ala Leu  
 225                                      230                                      235                                      240

<210> 37  
 <211> 1152  
 <212> DNA  
 <213> Homo sapiens

<220>  
 <221> CDS  
 <222> (1)..(1152)  
 <223>



&lt;400&gt; 37

cta aat caa caa gaa aac agg aac aga gat tta gga aga gag att gaa	48
Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu	
1 5 10 15	
aac ctc act aag gag tta gag agg tac cgg cat ttc agt aag agc ctc	96
Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu	
20 25 30	
agg cct agt ctc aat gga aga aga att tcc gat cct caa gta ttt tct	144
Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser	
35 40 45	
aaa gaa gtt cag aca gaa gca gta gac aat gaa cca cct gat tac aag	192
Lys Glu Val Gln Thr Glu Ala Val Asp Asn Glu Pro Pro Asp Tyr Lys	
50 55 60	
agc ctc att cct ctg gaa cgt gca gtc atc aat ggt cag tta tat gag	240
Ser Leu Ile Pro Leu Glu Arg Ala Val Ile Asn Gly Gln Leu Tyr Glu	
65 70 75 80	
gag agt gag aat caa gac gag gac cct aat gat gag gga tct gtg ctg	288
Glu Ser Glu Asn Gln Asp Glu Asp Pro Asn Asp Glu Gly Ser Val Leu	
85 90 95	
tcc ttc aaa tgc agc cag tct act cca tgt cct gtt aac aga aag cta	336
Ser Phe Lys Cys Ser Gln Ser Thr Pro Cys Pro Val Asn Arg Lys Leu	
100 105 110	
tgg att ccc tgg atg aaa tcc aag gag ggc cat ctt cag aat gga aaa	384
Trp Ile Pro Trp Met Lys Ser Lys Glu Gly His Leu Gln Asn Gly Lys	
115 120 125	
atg caa act aaa ccc aat gcc aac ttt gtg caa cct gga gat cta gtc	432
Met Gln Thr Lys Pro Asn Ala Asn Phe Val Gln Pro Gly Asp Leu Val	
130 135 140	
cta agc cac aca cct ggg cag cca ctt cat ata aag gtt act cca gac	480
Leu Ser His Thr Pro Gly Gln Pro Leu His Ile Lys Val Thr Pro Asp	
145 150 155 160	
cat gta caa aac aca gcc act ctt gaa atc aca agt cca acc aca gag	528
His Val Gln Asn Thr Ala Thr Leu Glu Ile Thr Ser Pro Thr Thr Glu	
165 170 175	
agt cct cac tct tac acg agt act gca gtg ata ccg aac tgt ggc acg	576
Ser Pro His Ser Tyr Thr Ser Thr Ala Val Ile Pro Asn Cys Gly Thr	
180 185 190	
cca aag caa agg ata acc atc ctc caa aac gcc tcc ata aca cca gta	624
Pro Lys Gln Arg Ile Thr Ile Leu Gln Asn Ala Ser Ile Thr Pro Val	
195 200 205	
aag tcc aaa acc tct acc gaa gac ctc atg aat tta gaa caa ggc atg	672
Lys Ser Lys Thr Ser Thr Glu Asp Leu Met Asn Leu Glu Gln Gly Met	
210 215 220	

tcc cca att acc atg gca acc ttt gcc aga gca cag acc cca gag tct 720  
 Ser Pro Ile Thr Met Ala Thr Phe Ala Arg Ala Gln Thr Pro Glu Ser  
 225 230 235 240  
 tgt ggt tct cta act cca gaa agg aca atg tcc cct att cag gtt ttg 768  
 Cys Gly Ser Leu Thr Pro Glu Arg Thr Met Ser Pro Ile Gln Val Leu  
 245 250 255  
 gct gtg act ggt tca gct agc tct cct gag cag gga cgc tcc cca gaa 816  
 Ala Val Thr Gly Ser Ala Ser Ser Pro Glu Gln Gly Arg Ser Pro Glu  
 260 265 270  
 cca aca gaa atc agt gcc aag cat gcg ata ttc aga gtc tcc cca gac 864  
 Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp  
 275 280 285  
 cgg cag tca tca tgg cag ttt cag cgt tca aac agc aat agc tca agt 912  
 Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser  
 290 295 300  
 gtg ata act act gag gat aat aaa atc cac att cac tta gga agt cct 960  
 Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro  
 305 310 315 320  
 tac atg caa gct gta gcc agc cct gtg aga cct gcc agc cct tca gca 1008  
 Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala  
 325 330 335  
 cca ctg cag gat aac cga act caa ggc tta att aac ggg gca cta aac 1056  
 Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn  
 340 345 350  
 aaa aca acc aat aaa gtc acc agc agt att act atc aca cca aca gcc 1104  
 Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala  
 355 360 365  
 aca cct ctt cct cga caa tca caa att aca gta agt aat ata tat aac 1152  
 Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Ser Asn Ile Tyr Asn  
 370 375 380

<210> 38  
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 <213> Homo sapiens

<400> 38

Leu Asn Gln Gln Glu Asn Arg Asn Arg Asp Leu Gly Arg Glu Ile Glu  
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Asn Leu Thr Lys Glu Leu Glu Arg Tyr Arg His Phe Ser Lys Ser Leu  
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Arg Pro Ser Leu Asn Gly Arg Arg Ile Ser Asp Pro Gln Val Phe Ser

35	40	45																	
Lys	Glu	Val	Gln	Thr	Glu	Ala	Val	Asp	Asn	Glu	Pro	Pro	Asp	Tyr	Lys				
50						55					60								
Ser	Leu	Ile	Pro	Leu	Glu	Arg	Ala	Val	Ile	Asn	Gly	Gln	Leu	Tyr	Glu				
65					70					75					80				
Glu	Ser	Glu	Asn	Gln	Asp	Glu	Asp	Pro	Asn	Asp	Glu	Gly	Ser	Val	Leu				
				85					90					95					
Ser	Phe	Lys	Cys	Ser	Gln	Ser	Thr	Pro	Cys	Pro	Val	Asn	Arg	Lys	Leu				
			100					105					110						
Trp	Ile	Pro	Trp	Met	Lys	Ser	Lys	Glu	Gly	His	Leu	Gln	Asn	Gly	Lys				
		115					120					125							
Met	Gln	Thr	Lys	Pro	Asn	Ala	Asn	Phe	Val	Gln	Pro	Gly	Asp	Leu	Val				
		130				135					140								
Leu	Ser	His	Thr	Pro	Gly	Gln	Pro	Leu	His	Ile	Lys	Val	Thr	Pro	Asp				
145					150					155					160				
His	Val	Gln	Asn	Thr	Ala	Thr	Leu	Glu	Ile	Thr	Ser	Pro	Thr	Thr	Glu				
				165					170					175					
Ser	Pro	His	Ser	Tyr	Thr	Ser	Thr	Ala	Val	Ile	Pro	Asn	Cys	Gly	Thr				
			180					185					190						
Pro	Lys	Gln	Arg	Ile	Thr	Ile	Leu	Gln	Asn	Ala	Ser	Ile	Thr	Pro	Val				
		195					200					205							
Lys	Ser	Lys	Thr	Ser	Thr	Glu	Asp	Leu	Met	Asn	Leu	Glu	Gln	Gly	Met				
	210					215					220								
Ser	Pro	Ile	Thr	Met	Ala	Thr	Phe	Ala	Arg	Ala	Gln	Thr	Pro	Glu	Ser				
225				230					235						240				
Cys	Gly	Ser	Leu	Thr	Pro	Glu	Arg	Thr	Met	Ser	Pro	Ile	Gln	Val	Leu				
				245					250					255					
Ala	Val	Thr	Gly	Ser	Ala	Ser	Ser	Pro	Glu	Gln	Gly	Arg	Ser	Pro	Glu				
			260					265					270						

Pro Thr Glu Ile Ser Ala Lys His Ala Ile Phe Arg Val Ser Pro Asp  
 275 280 285

Arg Gln Ser Ser Trp Gln Phe Gln Arg Ser Asn Ser Asn Ser Ser Ser  
 290 295 300

Val Ile Thr Thr Glu Asp Asn Lys Ile His Ile His Leu Gly Ser Pro  
 305 310 315 320

Tyr Met Gln Ala Val Ala Ser Pro Val Arg Pro Ala Ser Pro Ser Ala  
 325 330 335

Pro Leu Gln Asp Asn Arg Thr Gln Gly Leu Ile Asn Gly Ala Leu Asn  
 340 345 350

Lys Thr Thr Asn Lys Val Thr Ser Ser Ile Thr Ile Thr Pro Thr Ala  
 355 360 365

Thr Pro Leu Pro Arg Gln Ser Gln Ile Thr Val Ser Asn Ile Tyr Asn  
 370 375 380